1980

Progress Report No. 16

Biomedical Computer Laboratory

PROGRESS REPORT

No. 16

1 July 1979 — 30 June 1980

Biomedical Computer Laboratory

Washington University School of Medicine

700 South Euclid Ave.

St. Louis, Missouri 63110

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 16

JULY 1, 1979 - JUNE 30, 1980

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes activities during the period from July 1, 1979 through June 30, 1980. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine and its affiliated hospitals in the application of advanced computer techniques to problems in biology and medicine. This often requires work in areas stretching from basic physiology through mathematical models to equipment design. Our orientation is interdisciplinary with the recognition that effective communication for workers with differing backgrounds comes only through extended collaboration and mutual respect.

The vigorous development and evolution of specialized computer systems for use in the solution of research and clinical problems has continued to be the central focus of BCL activities. Several systems now in clinical use have seen a progression from exploratory pilot studies, to major developmental project, to local clinical trial, to clinical trials in multiple locations, to public availability through commercial manufacture. Perserverance in this sometimes tedious chain of development has found reward in the effective fielding of specialized computer systems to the medical community.

One class of computer applications requires strong coupling of the computer to its environment for digital signal processing. These applications typically involve the use of commercially available minicomputers and microprocessors in conjunction with specialized hardware designed and built locally. We have pursued many such applications by bringing signals from hospital wards and research laboratories to BCL by means of either analog or digital tape recordings or telephone lines and, more frequently, by taking the computers to the investigator's laboratory or the patient's bedside.

For those classes of applications dominated by information processing requirements, provisions have matured from telephone lines linking our minicomputers to the IBM System/360-370 at the Washington University Computing Facilities, through development and support of a minicomputer based MUMPS system, to the establishment of independent groups such as the Medical Computing Facility and the Medical Computing Service Group which serve the local medical complex. Diverse needs continue to be met by these various options while collaborative work continues on more advanced information-processing developments.

Still another class of applications requires extensive use of large-scale computational services. Many investigators are assisted in their research through the use of generalized numerical, non-numerical, and statistical routines. This work is carried out in part by staff members of BCL, but primarily by members of the Division of Biostatistics under the direction of Dr. Dabeeru C. Rao, and the University Computing Facilities whose director is Robert J. Benson.

The BCL enjoys collaboration with over 15 departmental divisions within the medical school but also finds support and enrichment through close ties with other facilities throughout the University. These arrangements are of benefit both to the BCL and to graduate students who find projects and employment among the activities in the laboratory. The Department of Computer Science is under the direction of Dr. Jerome R. Cox, Jr., past Director of the BCL. Close collaboration with the department currently emphasizes the area of information systems. Strong ties with the Department of Electrical Engineering are sustained through the Engineering School's Biomedical Engineering Program and common interests in digital signal processing techniques. The Department of Electrical Engineering is chaired by Dr. Donald L. Snyder, past Associate Director of BCL.

The Washington University Computer Laboratories is a federation of two research laboratories and two working groups which brings together the interests and resources of major segments of the University. The Biomedical Computer Laboratory is a component of the Medical School. The Computer Systems Laboratory is organizationally directly under the Chancellor. Both BCL and CSL share staff members with the Medical School and the School of Engineering and Applied Science. The Information Systems Group is housed within the Department of Computer Science and the Systems Design Aids Group is housed within the Department of Electrical Engineering.

The Coordinating Committee for the Washington University Computer Laboratories is charged with the task of monitoring long-term interactions between programs. The present composition of the Coordinating Committee is:

J. R. Cox, Jr., (Chairman) Principal Investigator for the Resource and Chairman, Computer Science
R. J. Benson, Director, University Computing Facilities and Assistant Vice Chancellor
S. B. Guze, Vice Chancellor for Medical Affairs
E. L. MacCordy, Associate Vice Chancellor of Research
J. M. McKelvey, Dean, School of Engineering and Applied Science
C. E. Molnar, Director, Computer Systems Laboratory
D. L. Snyder, Chairman, Electrical Engineering
L. J. Thomas, Jr., Director, Biomedical Computer Laboratory
D. F. Wann, Group Leader, System Design Aids

To aid in long-range planning of the health-related activities of the Washington University Computer Laboratories, a National Advisory Panel meets periodically with the Coordinating Committee. Particular attention is given to the confluence of important needs in biology and medicine with the technical advances capable of meeting these needs. Successful developments by WUCL may suggest implementation on a larger, perhaps national scale. The present composition of the National Advisory Panel is:

P. H. Abbrecht, Professor of Physiology and Internal Medicine, Uniform Services University of the Health Sciences, Bethesda, Maryland

H. L. Bleich, Associate Professor of Medicine, Harvard University

W. A. Clark, Consultant and former Director of CSL, Cambridge, Massachusetts

J. N. Gray, IBM Research Laboratories, San Jose, California

F. E. Heart, Bolt, Beranek & Newman, Cambridge, Massachusetts

D. M. Kipnis, Professor and Chairman, Department of Internal Medicine, Washington University

B. W. Matthews, Professor of Physics and Director of the Institute of Molecular Biology, University of Oregon

J. M. Smith, Computer Corporation of America, Cambridge, Massachusetts

E. A. Stead, Jr., Professor of Medicine, Duke University

C. Vallbona, Professor and Chairman, Department of Community Medicine, Baylor College of Medicine

II. SOURCES OF SUPPORT

During the period covered by this report the primary source of support for the Biomedical Computer Laboratory was a grant from the National Institutes of Health, Division of Research Resources.

RR 00396 A Resource for Biomedical Computing.

A research grant to study the relationship of arrhythmias and sudden death sponsored by the National Heart, Lung and Blood Institute has continued, in collaboration with the Department of Medicine and the Jewish Hospital.

HL 18808 Prediction and Prevention of Sudden Cardiac Death.

A subcontract was continued by the American Heart Association under NHLBI Contract NO1 HV 72989 to develop a database for arrhythmia detector evaluation.

Another subcontract was continued by the University of Rochester under NHLBI grant HL 22982 to support establishment of a Multicenter Post-coronary Risk Stratification Program.

NHLBI contract NO1 HV 72941 continues to fund a Holter Monitoring Core Laboratory to support a Multicenter Investigation of Limitation of Infarct Size.

Collaborative research continues with St. Louis University, under NHLBI Contract NO1 HV 62960, to establish a data management system and with the Jewish Hospital of St. Louis for research sponsored by their contract with Sandoz-Wander, Inc.

NCHSR grant HS 03792 was awarded to develop a medical information systems design methodology in the Computer Science Department and this laboratory.

Collaboration with other investigators often involved work already supported by other grants.

Public Health Services grants.

CA 04483 Effects of X-rays on Normal and Malignant Cells,

EY 00256 Factors Affecting Intraocular Pressure,

EY 00336 Glaucoma Clinical Research Center,

EY 02044 Automated Digital Processing of the Human Visual Field,

HD 09998 Clinical Correlations to Vitamin D Status in Infants,

HL 07081	Multi Disciplinary Heart and Vascular Diseases,
HL 13851	Cyclotron Produced Isotopes in Biology and Medicine,
HL 17646	Study of Ischemic Heart Disease,
HL 18144	Preprocessor System for Cardiograms,
HL 24394	Clinical Trial of Nifedipine During Cardiac Surgery,
MH 31054	Mental Health in the Aged: Biomedical Factors,
NS 03856	Auditory Communication and Its Disorders,
NS 06833	An Interdisciplinary Stroke Program,
NS 06947	Bioelectric Studies of Cerebral Cortex,
NS 14834	Mechanisms of Seizures and Anticonvulsant Drugs,
NS 15070	Regeneration and Functional Recovery in Cerebral Cortex.

III. PERSONNEL

EMPLOYEES

Personnel employed by the Biomedical Computer Laboratory during the period covered by this report were:

Director

Lewis J. Thomas, Jr., M.D., and Associate Professor of Anesthesiology, Physiology and Biophysics, Biomedical Engineering, and Electrical Engineering

Associate Director

G. James Blaine III, D.Sc., and Affiliate Associate Professor of Electrical Engineering and Computer Science *

Assistant Director

V. W. Gerth, Jr., M.S. *

Senior Research Associate

Jerome R. Cox, Jr., Sc.D., and Chairman, Computer Science, Professor of Computer Science, Electrical Engineering, and Biomedical Engineering in Physiology and Biophysics, Senior Research Associate, Computer Systems Laboratory

Business Manager

Virginia M. Bixon, B.S.

Research Associates

Robert J. Arnzen, Ph.D., and Computer Systems Laboratory
R. Martin Arthur, Ph.D., and Associate Professor of Electrical Engineering
Kenneth W. Clark, M.S.
James G. Dunham, Ph.D., and Assistant Professor of Electrical Engineering
A. Maynard Engebretson, D.Sc., and Central Institute for the Deaf
Ronald W. Hagen, M.S., and Surgery (Cardiothoracic Surgery)
Richard E. Hitchens, B.S., and Lecturer in Computer Science
William F. Holmes, Ph.D., and Associate Professor of Biological Chemistry
Kenneth B. Larson, Ph.D.

* In March of 1980 V. W. Gerth, Jr. left the Laboratory and G. James Blaine III, who had served as an Assistant Director since 1974, was promoted to Associate Director.

James G. Miller, Ph.D., and Professor of Physics, and Associate Director for Biomedical Physics, Laboratory for Ultra-Sonics, and Research Assistant Professor of Medicine
Donald L. Snyder, Ph.D., and Chairman and Professor of Electrical Engineering

Visiting Scientist

Harold W. Shipton, C.Eng., and Electrical Engineering

Research Assistants

H. Dieter Ambos, and Medicine (Cardiology)
David E. Beecher, M.S.
Gary H. Brandenburger, M.S.
Michael W. Browder, M.S.
Christopher N. Carlson, B.S.
Wen-Chang Chen, M.A.
Nian C. Cheng, M.S.
Stanley A. Garfield, B.S.
Alexander J. Gray, B.S.
Robert H. Greenfield, D.Sc., and Research Assistant Professor of Ophthalmology
Ross K. Hartz, M.S.
Russell E. Hermes, B.S.
Janet A. Johnson, M.S.
Margaret C. Jost, M.S.
John R. Klepper, Ph.D.
Ricardo G. Kortas, M.D.
Joanne Markham, M.S.
J. Stevadson Massey, B.A.
M. Michael Maurer, Jr., M.D., and Assistant Professor of Pediatrics
Charles N. Mead, M.D.
J. Philip Miller, A.B., and Assistant Professor of Biostatistics in Preventive Medicine
James K. Montrose, M.S.
Patricia Moore, Ph.D.
Jack G. Mottley, M.S.
Nizar A. Mullani, B.S., and Research Associate in Radiology
Michael A. Province, M.A., and in Biostatistics
Heino R. Pull, B.S.
Wayne R. Roloff, B.S.
Kenneth B. Schechtman, Ph.D.
Bert H. Tanaka, B.S.
Budimir Zvolanek, M.S.

Engineering Assistants

Stanley R. Phillips
Timothy L. Weadon, B.S.

Technical Assistants

Linda L. Brandenburger, R.N.
Margaret Buckley
Jing-Shiang Cheng, M.S.
Diane E. Coffey
Ellen M. Friedman, M.S., and in Biostatistics
Kathleen A. Madden, B.A.
Melissa A. Marlo
Mary P. McInnis
Patrick W. McLear
Stephen M. Moore
Stephen J. Potter
Steven R. Prothero, B.S.
Chung-Dak Shum
Donald W. Stein, Jr.
Camile A. Stelzer, B.S.
Donald A. Terovich, B.A.
Eufaula Thornton
J. Randall Thompson
James S. Wallis

Electronic Technicians

Theron R. Baird
Louis F. Combrevis
Joseph H. Flacke
Michael J. Rainey

Librarian

Monica W. Shieh, M.L.S.

Secretaries

Rebecca J. Bozesky
Jill D. Buchholz
Elizabeth A. Dennis
Shirley A. Gonzalez-Rubio
Celeste J. O'Rourke
Polly E. Raith

The following members from other departments and divisions have joint appointments with the Biomedical Computer Laboratory to facilitate collaboration and enhance interdisciplinary research:

G. Charles Oliver, M.D., Associate in the Biomedical Computer Laboratory, Professor of Medicine and Chief, Cardiology Division, Jewish Hospital
Rexford L. Hill, III, M.S., Research Associate in the Biomedical Computer Laboratory and Assistant Professor of Computer Applications in Radiology

Carol S. Higgins, A.B., Research Assistant in the Biomedical Computer Laboratory and Research Associate in Radiology

In addition, the following people worked at the laboratory for brief periods:

David M. Arbo, B.S.
Catherine A. Branyan
John A. Filla
John R. Hamm, Ph.D.
Thomas L. Hammonds
G. Howard Hays, Jr., B.A.
William R. Hosmon, B.S.
David M. McGraw
James T. O'Connor
Eric Thompson, B.S.
Kenneth G. Williams

RESEARCH COLLABORATORS

During the period covered by this report the following investigators from other laboratories, departments, or institutions, collaborated with BCL staff members on problems of joint interest.

J. Achtenberg, A.B., Medicine
R. L. Allen, M.S., Electrical Engineering
W. E. Ball, D.Sc., Computer Science
C. D. Barry, Ph.D., Computer Systems Laboratory
D. Bauwens, M.D., Medicine
B. Becker, M.D., Ophthalmology
W. L. Becker, Ophthalmology
R. J. Benson, J.D., Computing Facilities
L. D. Berenbom, M.D., Medicine
S. R. Bergmann, Ph.D., Medicine
G. E. Bickmore, Radiology
D. R. Biello, M.D., Radiology
S. B. Boxerman, D.Sc., Health Care Administration and Planning Program
M. M. Buckley, Pediatrics
K. R. Cash, Medicine
B. K. Clark, B.S., Cardiothoracic Surgery
R. E. Clark, M.D., Cardiothoracic Surgery
L. A. Coben, M.D., Neurology
R. D. Cohen, M.D., Medicine
P. B. Corr, Ph.D., Medicine and Pharmacology
W. A. Crafford, M.D., Medicine
R. M. Doroghazi, M.D., Medicine
A. A. Ehsani, M.D., Medicine
J. O. Eichling, Ph.D., Radiology
D. L. Elliott, Ph.D., Systems Science and Mathematics
G. J. Ehrhardt, Ph.D., Radiology
R. G. Evens, M.D., Radiology

D. C. Ficke, B.S., Radiology
O. Fukuyama, M.D., Medicine
M. H. Gado, M.D., Radiology
E. Gaelig, R.N., Medicine
G. G. Garcia, Barnes Hospital
W. D. Gillette, Ph.D., Computer Science
E. M. Geltman, M.D., Medicine
S. A. Golden, B.S., Neurological Surgery
D. W. Goldfarb, Computer Science
S. Goldring, M.D., Neurological Surgery
W. J. Grodzki, Jr., D.D.S., Ophthalmology
R. L. Grubb, Jr., M.D., Neurological Surgery
K. V. Gurumurthy, M.S., Electrical Engineering
S. N. Hack, M.S., Medicine
E. B. Hagelstein, B.S., Electrical Engineering
W. M. Hart, Jr., M.D., Ph.D., Ophthalmology
A. Hernandez, M.D., Pediatrics
R. R. Heye, M.S., Radiology
L. S. Hillman, M.D., Pediatrics
J. T. Hood, B.S., Radiology
J. T. Hood, Jr., Radiology
S. Igielnik, Ph.D., Medical Computing Facilities
A. S. Jaffe, M.D., Medicine
G. C. Johns, B.S., Computer Systems Laboratory
E. G. Jones, M.D., Ph.D., Anatomy
R. G. Jost, M.D., Radiology
M. A. Kass, M.D., Ophthalmology
B. Kumar, M.D., Radiology
S. Lang, Ph.D., Physiology and Biophysics
B. E. Laux, B.S., Radiology
J. Y. Lee, Ph.D., Biostatistics
R. A. Lerch, M.D., Medicine
P. A. Ludbrook, M.D., Medicine
A. T. Marmor, M.D., Medicine
R. E. Marshall, M.D. Pediatrics
L. A. Martin, C.P.N.P., Pediatrics
C. J. Mathias, B.A., Radiology
M. M. Maurer, Jr., M.D., Pediatrics
T. R. Miller, M.D., Radiology
J. W. Mimbs, M.D., Medicine
C. E. Molnar, Sc.D., Computer Systems Laboratory
T. H. Morrison, B.S., Electrical Engineering
R. A. Moses, M.D., Ophthalmology
D. W. Murch, B.A., Pathology
M. O'Donnell, Ph.D., Physics
R. E. Olson, A.A.S., Computer Systems Laboratory
M. V. Olson, M.D., Genetics
D. S. Payne, Medicine
A. J. Perejda, Ph.D., Pathology
C. A. Pérez, M.D., Radiology
C. F. Pieper, M.S., Neurological Surgery

S. C. Prasad, Ph.D., Radiology
J. L. Price, Ph.D., Anatomy
J. A. Purdy, Ph.D., Radiology
M. E. Raichle, M.D., Radiology and Neurology
J. L. Roberts, M.D., Pediatrics
R. Roberts, M.D., Medicine
A. Roos, M.D., Physiology and Biophysics
F. U. Rosenberger, D.Sc., Computer Systems Laboratory
J. E. Saffitz, M.D., Pathology and Medicine
S. J. Salmons, P.N.P., Pediatrics
M. J. Schlessinger, Microbiology and Immunology
S. M. Scott, M.D., Pediatrics
D. P. Schreiter, B.S., Medical Computing Facilities
B. A. Siegel, M.D., Radiology
D. W. Snyder, M.D., Medicine
B. E. Sobel, M.D., Medicine
S. P. Sutera, Ph.D., Mechanical Engineering
M. M. Ter-Pogossian, Ph.D., Radiology
T. J. Tewson, Ph.D., Radiology
A. J. Tiefenbrunn, M.D., Medicine
R. G. Tilton, Ph.D., Pathology
L. J. Tolmach, Ph.D., Anatomy and Radiology
J. R. Udell, B.S., Pathology
J. L. Vacek, M.D., Medicine
D. F. Wann, D.Sc., Electrical Engineering
I. R. Weinstein, M.D., Medicine
M. J. Welch, Ph.D., Radiology
C. S. Weldon, M.D., Cardiothoracic Surgery
R. Wette, D.Sc., Biostatistics
P. M. Wheelock, Medicine
J. R. Williamson, M.D., Pathology
F. X. Witkowski, M.D., Medicine
K. F. Wong, M.S., Computer Science
T. A. Woolsey, M.D., Anatomy

Baptist Memorial Hospital, Memphis, Tennessee

R. S. Gordon, B.A.

Central Institute for the Deaf, St. Louis, Missouri

D. H. Eldredge, M.D.
G. Friedman, M.S.
R. Glaesner
M. T. Hakkinen
I. J. Hirsh, Ph.D.
R. G. Karzon, M.A.
J. L. Lauter, Ph.D.
J. D. Miller, Ph.D.
R. B. Monsen, Ph.D.
D. A. Ronken, Ph.D.

M. Skinner, Ph.D.
J. P. Tadlock
N. R. Vemula, D.Sc.

Columbia University, New York, New York

J. T. Bigger, Jr., M.D.

Creighton University, Omaha, Nebraska

F. M. Nolle, D.Sc.
A. Zencka, M.D.

Dalhousie University, Halifax, Nova Scotia

J. Sherwood

Duke University Medical Center, Durham, North Carolina

D. B. Hackel, M.D.

Erasmus University, Rotterdam, The Netherlands

K. L. Ripley, M.S.

Indiana University School of Medicine, Indianapolis, Indiana

C. Fisch, M.D.
S. B. Knoebel, M.D.

Jewish Hospital, St. Louis, Missouri

L. L. Brandenburger, R.N.
B. R. Hieb, M.D.
J. R. Humphrey, R.N.
R. E. Kleiger, M.D.
R. J. Krone, M.D.
R. Ruffy, M.D.
S. Thanavaro, M.D.
P. T. Wallace

Massachusetts General Hospital, Boston, Massachusetts

H. K. Gold, M.D.
H. W. Strauss, M.D.

Mennen-Medical, Clarence, New York

J. A. Ritter, M.S.

Mitchell Humphrey and Co., St. Louis, Missouri

R. K. Stimac, B.S.

The MITRE Corporation, Bedford, Massachusetts

R. E. Zapolin, M.S.

Pennsylvania State University, University Park, Pennsylvania

D. B. Geselowitz, Ph.D.

Peter Bent Brigham Hospital, Boston, Massachusetts

E. Braunwald, M.D.

Research Triangle Institute, Research Triangle Park, North Carolina

W. K. Poole, M.D.

Roosevelt Hospital, New York, New York

H. M. Greenberg, M.D.

St. Louis University, St. Louis, Missouri

S. M. Ayres, M.D.
M. Bland, R.N.
A. E. Dyer, R.N.
R. G. Evans, B.A.
S. A. Kaiser, R.N.
H. S. Mueller, M.D.

St. Luke's Hospital East, St. Louis, Missouri

R. Paine, M.D.

University of Illinois at Chicago Circle, Chicago, Illinois

R. Langendorf, M.D.

University of Iowa, Iowa City, Iowa

R. C. Arzbaecher, Ph.D.

University of Kentucky College of Medicine, Lexington, Kentucky

B. Surawicz, M.D.

University of Louisville School of Medicine, Louisville, Kentucky

N. C. Flowers, M.D.

University of Rochester School of Medicine, Rochester, New York

A. J. Moss, M.D.

University of Texas Health Science Center, Dallas, Texas

J. T. Willerson, M.D.

University of Vermont College of Medicine, Burlington, Vermont

D. S. Raabe, M.D.

Previous years have seen occasional collaborative efforts with various computer firms and equipment manufacturers. This year projects of joint interest have involved:

Mennen Medical, Clarence, New York and Hewlett-Packard, Waltham, Massachusetts - An arrhythmia monitoring system.

Sandoz-Wander, Inc., Hanover, New Jersey - A collaborative drug study.

IV. PHYSICAL RESOURCES

The Biomedical Computer Laboratory was formed on April 15, 1964 and the original staff moved into laboratory space at 700 South Euclid Avenue in Saint Louis next to the Washington University School of Medicine's main building complex. While the laboratory has remained at this location, the floor space has increased from an original 5,515 square feet (gross) to the present 18,000 square feet (gross). Collaborative activities have frequently produced situations in which BCL staff members and systems occupy other areas within the Washington University Medical Center at or near the site of project applications. Facilities for computational applications, laboratories, staff offices and a reference room are located within BCL. Other physical resources include a well-stocked electronics shop, a large inventory of electronic and computer test equipment, a variety of digital system modules and both digital and analog recording instruments.

The Laboratory has steadily increased its computing capabilities since the time when a single LINC (Laboratory Instrument Computer) provided the original staff with an opportunity to apply a digital computer to interesting problems in medicine and biology. The small stored-program LINC computer had been designed specifically for use in biological and medical laboratories where there was a requirement for strong coupling between the computer, the investigator and the experiment. That first LINC is still used for a few service functions at BCL. During the past sixteen years BCL has addressed diverse medical and biological problems for which digital computing techniques seemed promising and appropriate, and today BCL has interest and involvement in over one hundred minicomputer systems (representing twenty different makes and models) within the Washington University Medical Center. In addition to these systems, BCL has direct responsibility for several systems which include a complement of computing hardware and software from a variety of minicomputer system manufacturers. These resources include:

- PDP-11's from Digital Equipment Corporation
- TI-980's from Texas Instruments Incorporated
- PC-12's from Artronix, Inc.
- 135's from California Data Processors
- System 7 from International Business Machines Corporation
- MMS-X's from Computer Systems Laboratory

Access to an IBM 360/370 system at the Washington University Computing Facility and to a MUMPS system at the Medical Computing Facility is available through several data terminals. Microcomputers of the personal class have been incorporated into the design of research instrumentation systems and several special-purpose instrument designs use a microcomputer or a microprocessor chip set.

V. RESEARCH PROJECTS

Introductory Summary

The goal of the Biomedical Computer Laboratory (BCL) is the application of digital computing techniques to problems in medicine and biology. This often requires work in areas stretching from basic physiology through mathematical models and frequently to the design of specialized equipment. The Laboratory's capability to respond to a broad range of research needs is the direct result of long-standing BRP support. BCL's research program is organized into several major project areas with the staff grouped into teams whose interests are focused correspondingly. This year, 80 individual projects can be categorized in nine areas.

In the area of ischemic heart disease and ECG analysis, algorithm developments for high-speed ECG processing have continued progress toward a major revision of Argus with emphasis on frequency-domain analysis. A new QRS detector and delineator has passed an extensive evaluation with flying colors; and a recently developed strategy for supraventricular analysis has been shown to outperform commercially available state-of-the-art processing. Novel work in ST-segment analysis from long-term ECG recordings is still preliminary but it looks promising. Two ECG processing systems have full Argus/2H capability and are in heavy use for local, national, and international collaborative studies ranging from fundamental electrophysiology to large-scale clinical trials. A third system based on the IBM System/7 is being upgraded to match the others. During the past year, Argus/2H software has been exported to Mennen-Medical, Inc., Dalhousie University in Nova Scotia, and Erasmus University in the Netherlands. Also, two commercial firms have expressed interest in replicating Argus/2H. The American Heart Association database for the evaluation of dysrhythmia detectors is now nearly complete and it provides an impetus for core research to develop a model for detector-performance evaluation.

Collaborative work with the Department of Physics and the Division of Cardiology continues to address tissue characterization via ultrasound through quantitative studies of both reflection (backscatter) and transmission (attenuation and time of flight), with tomographic reconstructions providing assessment of the latter. A ray-tracing model of geometric acoustics has been developed and coupled with an empirical model of anisotropy to simulate wave propagation in tissue. The effects of reflection, refraction, and diffraction are included. Backscatter measurements have been correlated with collagen content in infarcted hearts in vitro and with drug-induced cardiomyopathy. Transmission scans of dog hearts have successfully imaged post-infarction scarring in remarkable detail, using both time-of-flight and attenuation parameters. The minimization of phase-cancellation effects through use of a locally developed acoustoelectric transducer, the inclusion of compensation for beam-width frequency dependence, and the application of adaptive beamforming have all been proven to be important techniques.

Positron-emission transaxial tomography (PETT) systems continue to advance in both experimental applications and technological developments. PETT IV is now in routine use in the Barnes Hospital coronary care unit, where clinical studies have shown that scintigraphically delineated wall-motion abnormalities correlate with irreversible metabolic dysfunction (regional failure of ^{11}C-palmitate uptake). During the past year, PETT IV has also been applied successfully to liver scanning, using a new radiopharmaceutical, ^{68}Ga-iron hydroxide colloid. Meanwhile, isolated-perfused-heart studies which anticipate the capability for quantifying dynamic tracer uptake and clearance, have used PETT V to test the feasibility of estimating regional myocardial blood flow. Recent results are encouraging. PETT VI, the newest generation scanner just now being completed, will provide high-resolution and rapid (one-second) scans for small-animal studies such as those mentioned above, but its primary application will be to extend current studies of regional blood flow and metabolism in the human brain. The rapid scanning capability of PETT VI is accomplished through the use of cesium fluoride rather than sodium iodide crystals in the scintillation detectors. As PETT VI nears completion, work is now beginning on the next generation scanner, "Super PETT," which will also employ CsF crystals plus a high-speed acquisition and preprocessing system to achieve sub-nanosecond coincidence-timing resolution. The primary significance is that it should be possible to achieve sufficient information on differential time-of-flight estimates for coincidences to achieve an order of magnitude improvement in sensitivity over conventional PETT scanners. Feasibility experiments have shown substantial improvements in image quality. Also, work is in progress to develop a non-deterministic model and to use the maximum-likelihood method of statistics for incorporating the time-of-flight data in image reconstructions.

Over the past year radiation treatment planning activities have moved on from establishing the physical validity of our "delta volume" method for computing three-dimensional absorbed-dose distributions in inhomogeneous media using differential scatter-air ratios. Work now focuses on the application of advanced digital systems with appropriate algorithmic modifications to render the method practical in the clinical setting. By distributing tasks between a TI 980B computer and restructured macromodules which capitalize on opportunities for parallelism, it appears that the entire dose distribution in a 4096 cm^3 volume can be calculated in about six minutes. As the system is being integrated, experiments are in progress for exploring ways to utilize the MMS-X display system for presentation of the dose distributions.

In the general area of systems for pathophysiologic studies, work on a clinical physiologic research system continues to be motivated by a need for a systematic and flexible approach to the application of microcomputers to acquisition and digital processing of physiologic signals. To this end, the IEEE-488 communication standard has been adopted to accomodate both locally designed and commercially available hardware components and software modules have been written to serve as a useful library to support applications needs. The past year has seen new applications to systems for neuroanatomical autoradiographic analysis and for acquiring

extracellular cardiac potentials. The inventories of software modules and hardware designs continue to grow. Other projects include an M6800 data-acquisition perimetry system which is now in active use for patient studies and a constant-area tomography system for tracking dynamic intraocular pressure changes, both in the Department of Ophthalmology.

In addition to participation in Information Systems Group (ISG) activities to develop fundamentally novel approaches to system design, BCL maintains active participation in the development of several databases for disease management and research. The neonatology database is of central importance because it serves as a challenging test bed for the ISG work by virtue of its need to represent complex medical information relations and because it accomodates data sharing among several investigators. Other BCL databases support management functions for collaborative clinical research in ischemic heart disease at both the local and national levels (multicenter clinical trials and epidemiological studies). In general, as the data management tasks are completed, the verified data are transferred to other systems for extensive statistical analyses. Within the Medical School Community at Washington University, BCL supports only those databases directly relevant to our research activities. Most others are implemented and maintained by the Medical Computing Facility (MCF), an administratively distinct service organization which was spawned by BCL in 1975. During the past year, BCL staff worked with the University's Computing Facilities, the Division of Biostatistics, and MCF to establish a new service facility, the Medical Computing Service Group (MCSG). The charge of MCSG is to augment and extend the functions of MCF by providing comprehensive support to biomedical investigators for the development, usage, management, and analysis of research databases.

Speech and hearing research continues a longstanding collaboration with the Central Institute for the Deaf. Recent emphasis has been on the development of digital instrumentation for studies to explore electrocutaneous stimulation as an alternative sensory modality for speech perception, for the measurement of glottal source characteristics of normal and deaf talkers, for the development of visual displays for lip-reading studies, and for psychoacoustic studies of speech perception. The latter studies are directed toward an understanding of the acoustic and neural transformations which occur at the cochlear level and that are important in speech perception. To that end, the spectral characteristics of natural vowel sounds have been studied with a psychophysical hearing model and a comprehensive study of the relative merits of methods of vowel normalization has been undertaken. It appears that vowels can be best discriminated by the log transform of their spectral "shapes." This provocative finding has suggested new directions to be taken in theories of vowel perception.

Several projects focus on various aspects of central nervous sytem diseases and electroencephalogram analysis in addition to those noted above which utilize PETT studies. A system for the collection and processing of averaged visual evoked potentials was completed during the year and is now in routine use for studies of senile dementia. The Laboratory has provided peripheral support for work in the Department of Neurological

Surgery to develop an automated system for monitoring EEGs of epileptic patients via indwelling electrodes. A prototype of a new system for analyzing neuroanatomical autoradiomicrographs is near completion. Studies of image-processing algorithms for counting individual silver grains in the radiographs have been initiated and detector-performance evaluations are planned for the near future.

Supporting activities span exploratory biomedical applications, system development aids, and digital hardware and software designs of general utility to other laboratory activities. An especially promising exploration is a new collaboration with the Department of Genetics to develop an automated electrophoretic gel reader in support of a global approach to physical mapping of eukaryotic DNA. The design of a cross assembler for the M6800 based on our previously developed FORTRAN cross-assembler (FOCRAS), the characterization of solid-state video imaging devices, and the extension of our generalized "universal storage device" to satisfy data acquisition needs on multiple projects are all examples of supporting activities.

Individual Projects

A. Ischemic Heart Disease and ECG Analysis

Many of the projects reported in this section represent long-standing work in signal analysis of the electrocardiogram (ECG) including algorithm development toward improving analysis of the ECG signal as well as applications of existing signal-analysis technology to the processing of tape-recorded ECGs acquired for local and multicenter studies. Algorithm development focuses on time- and frequency-domain measures which are likely to improve QRS-detection and QRS-classification performances. Higher-level algorithm development focuses upon more recent strategies for the detection of supraventricular arrhythmias and ST-segment-deviation changes. Current algorithms are used in two "Argus/2H" computer systems for rapid analysis of 24-hour, tape-recorded ECGs from a local clinical trial of nifedipine in cardioplegia, a multicenter investigation of limitation of infarct size, a multicenter post-infarction risk program, and a variety of smaller studies. One system is also used for the creation of the American Heart Association database of ventricular arrhythmias, work which has stimulated the formulation of a performance evaluation model which, in turn, might be used when automated analysis systems are evaluated with the database. The systems have been used since 1977-1978 when they succeeded a prototype Argus/H system which analyzed several thousand long-term ECGs for a natural history study of sudden death. Rigorous biostatistical analysis of that study is underway, and major findings to date are reported here. Interest in Argus/2H, here and abroad, has resulted in both partial and full export of its software.

BCL personnel are involved in many other local investigations of ischemic heart disease. Digital techniques applied to clinical echocardiography are reported in this section, whereas other ultrasonic work applied to tissue characterization is considered in section B. In other investigations, BCL involvement is less direct and of a more collaborative nature. These projects include enzyme-release kinetics, myocardial perfusion and metabolism, and electrophysiologic characterization of myocardial depolarization.

A-1. Argus Algorithm Development

Personnel: K. W. Clark, BCL
R. G. Kortas, BCL
P. W. McLear, BCL
C. N. Mead, BCL
S. M. Moore, BCL
S. J. Potter, BCL
L. J. Thomas, Jr., BCL
E. Thompson, BCL

Support: RR 00396

Long-range plans call for a complete revision of the Argus algorithms. The first step, development and evaluation of a new QRS detector/delineator, to replace the current Primitive, has been completed and reported.[1] Implementation of the new detector awaits completion of a revision of the Cycle algorithm for QRS classification. The present Cycle algorithm is limited to classifying beats as normal, PVC, abnormal (but not PVC), and borderline. The revised Cycle will assign only shapes, not labels, and will include a feedback loop to the new detector to supply Q-Q and S-S intervals of normal-shaped beats. A new algorithm, called "Sequence," will make final beat classification and incorporate logic from the current Cycle algorithm for PVC labeling, global logic using total tape cluster information adapted from machine-edit strategies for confirming Cycle-flagged PVCs as true-PVCs, and logic excerpts from recent work in the area of supraventricular dysrhythmic event detection. In addition to QRS detection and classification, algorithms to detect ST-segment changes are under investigation. The QRS detector, recent work in supraventricular dysrhythmia analysis, and early work in ST-segment analysis are reported here.

QRS detector/delineator. An evaluation data set consisted of more than 300,000 QRS complexes from 145 different waveform segments of 15 to 30 minutes duration. Each waveform segment was analyzed by the detector and the results reviewed on a beat-by-beat basis by one of four technicians using a special version of the Argus/2H edit program. In reviewing each detected complex, the technician indicated whether or not the candidate complex was a real event, P wave, T wave, or noise. For real events, the technician approved or disapproved of the detector's determination of both onset and termination. Real events missed by the detector were "inserted" by the technician. Individual beat information as well as all technician decisions were retained in machine-readable form so that machine-generated summaries were easily produced. The evaluation criteria were (1) false-positive rate, (2) false-negative rate, and (3) percentage of total beats measured correctly. The false-positive rate was computed as the number of P waves, T waves, and noise events detected as QRS complexes. The false-negative rate was computed from the number of technician-inserted beats. The complex was considered to be measured correctly if (a) either onset or termination was correct; (b) no "major" vectors of the complex were missing, and (c) no "major" vectors from surrounding P wave, T wave,

or noise were included in the complex. The term "major" was defined as greater than 30% of the largest vector of the complex. Of 301,292 QRS complexes from 131 recordings of one-half hour each, the detector's false-positive rate was 0.7%, false-negative rate was 0.1%, and correctly-measured rate was 99% (both onset and termination were correctly measured in 95% of the complexes). In a subset of 14 recordings which included 33,130 QRS complexes and which were chosen because the standard Argus detector found in them a significant percentage artifact, the new detector proved mildly superior to Argus in correct delineation and false-negative rate but especially superior in false-positive rate (2% vs. 9%). In a set of 14 recordings of 15 minutes each, supplied by Hewlett-Packard, which consisted of very-low-amplitude PVCs, the new detector also proved superior to the Argus detector. The lower false-positive rate should be of considerable interest to providers of false-alarm-ridden real-time monitoring systems; the lower false-negative rate would be especially important in the analysis of recorded long-term electrocardiograms.

Supraventricular dysrhythmia analysis. Early work in the detection of supraventricular dysrhythmic events (PR 15, A-1) has progressed and been reported.[2] At this point, the system routinely indicates the presence or absence of such events; an evaluation of frequency of individual beats and episodes has not yet been conducted. The procedural steps can be categorized as being either active or passive, from the computer's point of view, depending upon whether algorithmic computations on the Cycle stream data are required (active) or whether a simple search on a specified parameter suffices (passive).

Passive approaches include interactive review of suspiciously short and long intervals, shortest and longest Normal-Normal intervals, and fastest and slowest 5-beat heart rates. These methods are likely to uncover missed low-amplitude QRS complexes, bradycardias and tachycardias, 2nd and 3rd degree AV blocks, SPCs and SPC salvos, PST, escape beats, QRS-like noise spikes, signal dropouts, excessive baseline wander, and evidence of battery failure.

Active approaches focus on the forward coupling interval (FCI) and backward coupling interval (BCI) ratios (r = FCI/BCI) of Normal and Borderline beats. Dispersion of individual fifteen-minute frequency distributions of all $\{1/2 < r < 3/2\}$ is used to qualify the period as predominantly "normal-sinus rhythm," "sinus arrhythmia," or "atrial fibrillation." Periods of normal-sinus rhythm are more closely scrutinized to identify SPCs which then may be reviewed as true or false with an interactive SPC-edit program.

We regard our approach to background rhythms as still experimental and threshold values are mostly empirical. Meanwhile we are collecting a database sufficient for rigorous evaluation. Although the method appears to work where sinus arrhythmia or atrial fibrillation is the dominant rhythm, we have too few examples to test the response to paroxysms of either. These algorithms do nothing more than identify those waveforms and sequences of complexes which deserve the attention of the editor and

the scrutiny of the electrocardiographer, who may then differentiate between events such as atrial and junctional premature complexes. Supraventricular arrhythmias not specifically addressed by this strategy are: regular junctional rhythm, first degree heart block, atrial flutter, shifting atrial mechanism, atrial parasystole, and atrial fusion beats.

Because we have neither a large database of supraventricular arrhythmias annotated beat-by-beat nor the economic means to generate one, it has not been possible to perform a thorough evaluation of this strategy. We have compared our results, however, with those of the leading nationwide commercial scanning service in St. Louis. Sixty-four tapes were selected from those already processed by Argus/2H and sent to the scanning service for full processing, including cardiologic review. The method of tape selection was specifically designed to increase the probability that Argus/2H had missed a supraventricular event of interest. We had observed from the results of an earlier post-infarction study, that the best predictor of the arrhythmic content of an ambulatory recording is another recording from the same patient, even though separated by several months. Accordingly, we chose only those for which both 3-month and 6-month recordings were available and for which Argus/2H had identified a supraventricular arrhythmia on one but not the other and for which the arrhythmia in question could not be detected on the basis of heart rate alone. No instances of atrial fibrillation were represented in this subset.

Neither the scanning service nor their cardiologist has any connection with our institution and the purpose of the processing was not revealed until after all tapes and results were returned. Argus/2H outperformed the commercial scans: 92% versus 74% for the presence of SPCs and 94% versus 44% for the presence of SPC couplets and runs. Neither processing uncovered any episodes of paroxysmal supraventricular tachycardia, atrial fibrillation, or sinus arrhythmia and we have no independent evidence that any were present. Most of the recordings included significant ventricular ectopic activity; 47 showed multiform PVCs and 27 contained PVC couplets.

ST-segment changes. Automated ST-segment analysis in long-term ECG recordings has received little attention primarily because of lack of control over the calibration of the ECG during recording and playback. Calibration is of course crucial to the reporting of diagnostic statements of absolute millivolts of ST elevation or depression with which the physician is familiar. Nonetheless, significant ST-segment changes within a long-term ECG recording may warrant at least the attention of the physician. On that hypothesis, we began to formulate algorithms for detection of ST-segment changes within long-term ECG recordings.

Utilizing an edited Cycle data stream of beat labels and occurrence times, the first ST routine searches every 2 minutes of real-time-equivalent Cycle for 8 consecutive normal beats with stable interbeat intervals. The heart rate is computed and digital waveform samples for the octet are signal-averaged. The Aztec and Primitive data-reduction algorithms are run on the averaged waveform to specify QRS onset, termination, duration and height. Baseline is set as the first Aztec flat line of at least 16

milliseconds in the front of the QRS. The ST segment is defined as the curve of best fit through "x" points beginning "y" points beyond the QRS. Computed ST parameters are absolute elevation/depression, elevation/depression as a percent of QRS height (PQH), slope, and area. The metric PQH to some degree compensates for amplitude variations arising from signal-gain adjustments permitted the playback-device operator attempting to optimize performance of the arrhythmia detector.

A second ST routine displays a time-PQH histogram designed to reveal sustained or transient elevation/depression or gradual or abrupt changes. From the gross display, an operator may view the episode of maximum PQH or any other episode by setting a time-axis cursor. The secondary display includes the episode, an expanded view of the averaged complex with delineator tics for baseline and ST segment, and numerical measurements. Plots and printouts preserve display content.

A rigorous evaluation of the ST algorithms has been stymied by an inadequate database of interesting, bizarre, and challenging examples of ST-segment deviations. Extramural investigators have been solicited for such examples so that we can expand the database to test ST algorithms and future refinements to them.

1. C. N. Mead, K. W. Clark, S. J. Potter, S. M. Moore and L. J. Thomas, Jr., "Development and Evaluation of a New QRS-Detector/Delineator," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 79CH1462-1C, Geneva, Switzerland, pp. 251-254, September 26-28, 1979.

2. L. J. Thomas, Jr., K. W. Clark, C. N. Mead and J. W. Mimbs, "Supraventricular Arrhythmias: Strategies for Detection," in Ambulatory ECG Recording, Year Book Medical Publishers, in press.

A-2. High-Speed ECG Processing: Hardware

Personnel: R. E. Hitchens, BCL
S. M. Moore, BCL
T. L. Weadon, BCL

Support: RR 00396

Work has continued on the upgrade of IBM System/7 hardware (PR 15, A-2) in order to add peripheral support necessary to process and edit 24-hour 2-channel Holter recordings. A 160 megabyte disk system (PR 15, G-17) has been tested and diagnostic programs have been written. The cycle-steal 800/1600 bit-per-inch tape system has been designed, built and tested.

The design of an LSI-11 based high-speed oscilloscope display is under way. This system will be DMA refreshed from the LSI-11 memory, thus increasing the System/7 memory space available for programs. In addition, a cycle-steal analog-to-digital converter for ECG digitizing is planned.

A-3. High-Speed ECG Processing: Software

Personnel: K. W. Clark, BCL
S. M. Moore, BCL
S. J. Potter, BCL
H. R. Pull, BCL

Support: RR 00396
HL 18808
HL 22982
HV 72941

Operational software for the two Argus/2H systems has temporarily reached a stable state. No significant additions were made last year. In the near future, we expect to implement promising algorithms which are beyond the early stages of development and include a new QRS detector/delineator, supraventricular arrhythmia analysis, and ST-segment analysis (A-1).

The Argus/H system is being revamped into an Argus/2H-like system. A new operating system and file-handling software have been written (PR 15, A-3). A dual-density tape drive and two high-density disk drives were recently added; software utilities for use with those new devices have been written. Although the high-speed scan algorithms (Aztec, Primitive, Cycle) for processing long-term ECGs were originally written on the Argus/H system, they have been rewritten for more efficient processing. Near-future plans call for the writing of post-scan programs necessary for complete processing and editing.

A-4. Holter Tape Processing

Personnel: K. W. Clark, BCL
H. D. Ambos, BCL
T. L. Hammonds, BCL
W. R. Hosman, BCL
K. A. Madden, BCL
M. A. Marlo, BCL
D. A. Terovich, BCL
D. E. Coffee, BCL

Support: RR 00396
HL 18808
HL 22982
HV 72941

While the Argus/H system undergoes hardware and software reorganization (A-2, A-3), only the two Argus/2H systems are used for processing long-term (Holter) ECG recordings. These two systems are used primarily for the Multicenter Investigation of Limitation of Infarct Size (MILIS) (A-21) and the Multicenter Post-Infarction Program (MPIP) (A-19). The tape processing protocols for these studies were described last year (PR 15, A-4). The total number of tapes analyzed for these ongoing studies is 772 (MILIS) and 367 (MPIP). Data management support for these projects is described elsewhere (D-8). The systems have also been used for an efficacy study of LB-46 (Prindolol) (PR 14, A-6) and a clinical trial of nifedipine in cardioplegia (A-22). Systems time not used to process recordings is dedicated to algorithm development (A-1).

A-5. Argus Exportation

Personnel: K. W. Clark, BCL
R. E. Hitchens, BCL
C. N. Mead, BCL
S. M. Moore, BCL
K. L. Ripley, M.S., Erasmus University
J. A. Ritter, M.S., Mennen-Medical
J. Sherwood, Dalhousie University
L. J. Thomas, Jr., BCL

Support: RR 00396

The Argus/2H computer system for analysis of Holter-recorded ECGs was designed and assembled in a fashion we perceived as amenable to exportation to the commercial sector or at least to other research institutions. For one reason or another, system duplication never came to pass except for a local replication (PR 15, A-2) when we were charged with processing Holter recordings for a Multicenter Investigation of Limitation of Infarct Size (A-21). Nonetheless, we have been quite active in the dissemination of some of the Argus/2H algorithms and/or software.

Mennen-Medical has adapted the essence of the QRS detector/delineator (A-1) for use with their real-time monitoring system. Erasmus University has applied portions of the software to Holter-tape analysis for use in an international multicenter drug study. Dalhousie University is incorporating portions of the Argus/2H software into a Holter-tape analysis system whose hardware configuration is quite similar to that of Argus/2H. Several months were spent contributing to a feasibility study by Digital Equipment Corporation on a high-volume Holter-tape processing system for Cardio-Bionic Scanning.

A-6. Extended Analysis of Argus/H and Argus/2H Quantified VEA

Personnel: J. P. Miller, BCL
K. W. Clark, BCL
E. M. Friedman, BCL
R. E. Kleiger, M.D., Jewish Hospital
S. M. Moore, BCL
G. C. Oliver, M.D., Medicine
M. A. Province, BCL
S. Thanavaro, M.D., Jewish Hospital

Support: RR 00396
HL 18808
HV 72941
Sandoz-Wander, Inc.

Following the processing and editing of Holter tapes by Argus/H or Argus/2H (A-4) the beat-by-beat annotation of the 10- or 24-hour recordings (Cycle streams) were accumulated on industry-compatible tape and transported to the IBM System/360-370 for bulk processing in order to extract salient features of the ventricular ectopic activity (VEA).

SUMMARY (PR 12, A-2), the PL/I program which runs on the System/360-370 and is designed to reduce the Cycle streams to variables of interest, was altered so that both Argus/H and Argus/2H created Cycle streams could be utilized to produce the expanded output for each PVC on the record (PR 15, A-6). The revised SUMMARY will then be utilized to reprocess the tapes acquired in the Sudden Death Study (A-7) to more fully understand the relationships among the various features of the ambulatory ECG and the type of VEA observed on the tapes.

A more extensive analysis of ventricular runs (3 or more consecutive PVCs) was completed. Of 1822 recordings obtained on 289 patients two weeks to twelve months post MI, 1464 had at least one PVC, and 136 (7.5%) had at least one run. Eighty-five of the tapes with runs (62.5%) had at least one episode of VTACH (runs with average rates over 120/minute), while 70 of them (51.5%) had at least one episode of AIVR (runs with rates under 120/minute). Since 20 of the 70 tapes with AIVR also had VTACH, it was questioned whether the conventional wisdom of AIVR being a benign arrhythmia was prudent. When the tapes were stratified by PVC rate, tapes with couplets, bigeminy, multiform PVCs or late PVCs (coupling intervals greater than 600 ms) carried an additional risk of runs, thus supporting the concept that complex VEA are associated among themselves, relatively independent of PVC rate (PR 15, A-6). R-on-T did not appear to carry this same independent risk, although PVCs with coupling intervals either less than 400 ms or more than 600 ms were more likely to initiate couplets or runs than PVCs of 400-600 ms.

Day-to-day variation estimates of some 65 of the Summary-program (PR 12, A-2) variables were also obtained, using 24-hour Holter recordings

made on eighteen patients enrolled in a double-blind, cross-over study on antiarrhythmic agent (VIB). For each patient, four recordings were utilized, two made within one-day intervals during the control phase, and two made within one-day intervals during the placebo phase. Thus, for each variable, a 36 degree-of-freedom estimate of the day-to-day variation within patients was obtained. These estimates can now be used in assessing the significance of the variations found in these variables across recordings made from the same patient (or different patients) throughout the year following their MI. The average PVC rate/hour (in log 10 scale) was found to have a within-patient standard deviation of .20. Similarly, the average couplet rate/hour and the average run rate/hour had standard deviations of (in log 10 scale) 0.24 and 0.29, respectively. The within-patient standard deviation for average heart rate (in beats/min) was 3.8, while the average non-PVC to PVC and average PVC to PVC coupling intervals in ms had within-patient standard deviations of 18 and 55, respectively. The intrapatient variances for PVC rate appears to be due largely to the Argus reprocessing error (PR 14, A-6) while heart rate is more reflective of changing day-to-day activity levels.

A-7. Natural History Study of Sudden Death

Personnel: G. C. Oliver, M.D., Medicine
L. L. Brandenburger, R.N., Jewish Hospital
K. W. Clark, BCL
J. R. Humphrey, R.N., Jewish Hospital
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
J. P. Miller, BCL
P. T. Wallace, Jewish Hospital
P. Moore, BCL
M. A. Province, BCL
S. Thanavaro, M.D., Jewish Hospital
L. J. Thomas, Jr., BCL
E. Thornton, BCL

Support: RR 00396
HL 18808
Barnes Hospital
Jewish Hospital

We have completed the clinical and demographic data collection on 2175 patients recovering from myocardial infarction. During the past year, we have thoroughly scrutinized the database, and believe we have uncovered and corrected all errors. A follow-up rate of 98.7% has been achieved.

Several important studies have examined the relationship between clinical features which characterize patients during their coronary care unit stay and their subsequent prognosis. The first focused on in-hospital mortality. We found that the type of infarction (transmural vs. non-transmural) was of only minor importance, if any, in predicting survival whereas the levels of serum enzymes (which reflect the amount of myocardium damaged) was of considerable importance. As a group, patients with non-transmural infarction had a lower in-hospital mortality (3% vs 11%, $p < 0.01$) but this difference was no longer significant if the analysis corrected for the higher SGOT levels present in patients with transmural infarction.

More recently we have investigated the long-term prognosis of the same patient population, again comparing patients with first transmural to those with first non-transmural infarct. We found that risk factors for death in the first year (measures of the amount of left ventricular damage) were not successful in predicting mortality 2-3 years after infarction. In contrast, at this late stage of recovery, patients with non-transmural infarcts, particularly those aged 65-75 years, had an extremely high death rate.

Other studies have identified clinical features which best predict the occurrence of runs of ventricular tachycardia during the year following an infarction. Using only data routinely available on patients during their coronary care unit stay we were able to divide patients into quartiles of risk. Those in the highest risk quartile had a ten-fold higher incidence of runs over those in the lowest quartile.

Finally, we evaluated the relationship between length of Holter recordings and the likelihood of detecting ventricular arrhythmias. We found that one hour of recording was insensitive for detecting complex arrhythmias except in patients with peak PVC rates of 30 or more per hour. Twelve hours of recording detected 92% of patients with complex PVC's (multiforms, couplets or runs), or high PVC rates, but only 76% of those with runs. Thus, the choice of an appropriate recording duration is highly dependent on the type of ventricular arrhythmia sought.

A-8. Development of the American Heart Association Database for Arrhythmia Detector Evaluation

Personnel: R. E. Hermes, BCL
R. M. Arthur, BCL
D. B. Geselowitz, Ph.D., Pennsylvania State University
M. P. McInnis, BCL
G. C. Oliver, M.D., Medicine
L. J. Thomas, Jr., BCL
E. Thornton, BCL

Support: RR 00396
HV 72989

This project has had as its goal the development of a database for the evaluation of automated ventricular arrhythmia detectors. The database consists of 160 digital tapes, each containing a digitized 3-hour segment of a two-channel ambulatory ECG recording. Each recording has been sampled at 250 samples per second, 12 bits per sample. Each QRS complex in the final half hour of each record is annotated on a beat-by-beat basis.

The database is divided into eight distinct arrhythmia classes. Each class, which contains 20 tapes, is further subdivided into two parts, a test set and a developmental set. This format allows evaluation of VAD performance on all or any select types of ventricular arrhythmias. The eight classes are No PVCs, Isolated Uniform PVCs, Isolated Multiform PVCs, Bigeminy, Couplets, R-on-T, Ventricular Rhythms, and Ventricular Fibrillation.

Assimilation of data for use in the database was handled by an organization of independent committees of well respected members of the cardiology community. Integral parts of the organization were the Tape Selection Committee, the Committee of Expert Electrocardiographers, and the Contributing Institutions. The Biomedical Computer Laboratory (BCL) has served as the center for the development of this database under the supervision of the American Heart Association Committee of Electrocardiography.

The Tape Selection Committee consists of four leading authorities on arrhythmias and arrhythmia detection: Dr. Robert C. Arzbaecher, University of Iowa; Dr. Nancy Flowers, University of Louisville; Dr. J. Thomas Bigger, Jr., Columbia University; and Dr. Suzanne Knoebel, Indiana University. Individual committee members, on regular visits to the BCL, chose candidate tapes for entry into the database. Then at periodic meetings of the entire committee, tapes were accepted to become part of the final database.

The expert electrocardiographers have annotated, individually, each tape selected for database inclusion. Members of this committee are: Dr. Charles Fisch, Indiana University; Dr. Borys Surawicz, University of Kentucky; and Dr. Richard Langendorf, University of Chicago. Not only

has this group annotated each beat of each record, but they have noted the noise contents and background rhythms contained in the tapes as well.

Two-channel ambulatory tapes were solicited from interested institutions. Seventeen major contributing institutions as well as several individual contributors have submitted a total of over four hundred tapes. The institutions are:

Contributing Institutions

Alleghany General Hospital	Pittsburgh, PA
William Beaumont Hospital	Royal Oak, MI
Cleveland Metro. General Hospital	Cleveland, OH
University Hospital	Copenhagen, Denmark
Cornell University	New York, NY
Creighton University	Omaha, NB
Danbury Hospital	Danbury, CT
Duke University	Durham, NC
Kyusha University	Fukuoka, Japan
Louisville Jewish Hospital	Louisville, KY
Institute of Cardiology	Montreal, Canada
Lariboisiere Hospital	Paris, France
Thoraxcentrum	Rotterdam, The Netherlands
University of California	Los Angeles, CA
University of California - V.A. Hosp.	San Diego, CA
Washington University	St. Louis, MO
Yale University	New Haven, CT

Rigorous protocols were established for the selection of the database tapes. First, contributors sent tapes to the BCL for preliminary processing by the Argus/2H system. A four-hour portion of each tape considered to be of sufficient quality and content was reviewed by a member of the Selection Committee. Of the more than 400 tapes submitted, 299 were reviewed by the Selection Committee. Those not reviewed were considered technically inadequate or contained insufficient arrhythmias for database inclusion.

The four-hour segments reviewed by individual members of the Selection Committee were either accepted, rejected, or held for later review. If a tape was accepted, a three-hour portion (from the four-hour record) was proposed as a candidate for the final database.

Tapes accepted during individual review were then reviewed by the full committee and were again either accepted, rejected, or held. Only those tapes accepted were sent to the Expert Electrocardiographers for annotation.

The last half hour of each tape accepted was written out on paper strips with each QRS complex indicated by a time of occurrence marker. These strips were sent independently to each of the three electrocardiographers who annotated each beat. Complete agreement among all electrocardiographers

was necessary before a beat annotation was accepted as final. Disagreements were resubmitted to the experts for re-examination and ultimate resolution. Currently, the database has 145 of the needed 160 tapes. With the use of the MECCA system (A-9) installed in the Jewish Hospital Medical Intensive Care Unit as well as various other resources, the rare tapes needed to complete the Ventricular Fibrillation and R-on-T classes should become available. Meanwhile final processing, documentation, and microfilming of all other tapes is continuing.

Efforts are being made to find a database distribution center which will act as a service organization for providing users of the database with copies of the database tapes and technical assistance. In addition, methods of distribution of the developmental tapes and associated documentation are being formulated.[1] Protocols for system evaluation using the test set of tapes are also under consideration. These plans for distribution and evaluation are expected to be complete before the final database is ready for release. Until then, a database tape format description and an example tape are being distributed to potential database users so that they may familiarize themselves with the database. The projected date for completion is December 31, 1980.

1. R. E. Hermes and G. C. Oliver, "Use of the American Heart Association Database," in Ambulatory ECG Recording, Year Book Medical Publishers, in press.

A-9. MECCA System

Personnel: R. E. Hermes, BCL
R. M. Arthur, BCL
B. R. Hieb, M.D., Jewish Hospital
S. R. Phillips, BCL

Support: RR 00396
HV 72989

A continuing effort has been made to make the MECCA system functional (PR 15, A-9). Many problems have had to be overcome because of the environment in which the system must function. The system is designed to collect 3 to 4 hours of ECG data on any 4 patients within the Jewish Hospital Medical Intensive Care Unit (MICU). Original plans called for four mobile ECG amplifier carts to be moved to the bedside of each patient to be monitored. This plan required MICU staff to move the carts from bedside to bedside as well as to apply an extra set of five electrodes to the patient and to connect a cable which transmitted the analog ECG signal to the computer. Each bedside is equipped with an alarm button to be used to signal the computer in the event that a threatening arrhythmia

had or was occurring. The alarm button was to be pressed by MICU personnel. This signal-acquisition scheme was tried for a short time, but had to be abandoned due to reluctance of MICU staff to connect and move the ECG carts and press the alarm button.

The system then remained idle for several months due to computer room construction. Meanwhile, a new method of connecting patients to the system was planned. We found that we could use the hospital's new analog ECG monitoring system to buffer and transmit the analog ECG signal back to the computer. This required neither the use of the ECG carts nor the application of extra electrodes to each patient. The bedside alarm buttons were replaced with a separate panel of alarm buttons on the monitoring console at the main nursing station. In the event that a monitor technician spotted an arrhythmia on the console ECG monitors, a simple press of a button within arm's length of the technician would signal the computer.

The new approach is more functional and independent of the MICU staff, with the exception of the monitor technician whose job is normally watching the main-station ECG monitor. We hope to have the system running routinely soon.

A-10. Assessment of Vascular Integrity of the Myocardium Following Ischemic Injury

Personnel: R. G. Tilton, Ph.D., Pathology
K. B. Larson, BCL
D. W. Murch, B.A., Pathology
A. J. Perejda, Ph.D., Pathology
J. R. Udell, B.S., Pathology
J. R. Williamson, M.D., Pathology

Support: RR 00396
HL 07081
HL 17646
The Kilo Diabetes and Vascular Research Foundation

We have continued our previously reported studies (PR 15, A-10) of the pathophysiology of ischemic injury to the heart. Our objectives are to characterize time-dependent effects of ischemic injury on membrane-permeability characteristics of the cardiac vasculature and musculature and to evaluate effects of drug interventions on the preservation of the coronary vasculature and musculature. The approach chosen for this investigation has been to use appropriate vascular- and extracellular-space markers labeled with gamma-emitting isotopes that can be monitored by external detection. Experiments are performed under constant-flow conditions using isolated rabbit hearts perfused with Krebs-Henseleit buffer containing

1-percent dialyzed bovine-serum albumin (BSA) and 0.5-percent dialyzed 300,000-MW polyvinyl pyrrolidone. Radioactive count-rate data are analyzed using mathematical models based on established principles of tracer kinetics.

Effects of reperfusion for 60 min following global ischemic injury of 15, 30, 45 and 60 min duration have been characterized using light and electron microscopy. Additional studies for comparing the effects of low-flow versus no-flow ischemic injury have also been initiated. A 30-min ischemic interval was chosen for evaluating drug interventions. Studies are now in progress to evaluate the protective effects of nifidipine, diltiazem and verapamil on the coronary vasculature and musculature. The choice of 30 min for the ischemic time interval was based on the following observations: 1) significant increases in the residual fraction of BSA remaining in the detector field (suggesting compromised vascular function), and 2) slight increases in left-ventricular end-diastolic pressure with recovery of left-ventricular developed pressure to 85 percent of the initial value (suggesting intact sarcolemmal membranes). A 5-min infusion to steady state of ^{125}I-BSA, ^{14}C-sucrose and ^{3}HOH terminates the reperfusion period and provides an independent assessment of the vascular-, extracellular-, and total-water spaces obtained by tracer-kinetic analysis of the external-detection data.

A-11. Physiologic Signal Processing

Personnel: C. N. Mead, BCL
J. S. Cheng, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396

During the past two years, we have been exploring the feasibility of utilizing frequency domain (FD) analysis in ECG classification algorithms, particularly with respect to the long-term Holter-ECG recordings which BCL currently analyzes entirely in the time domain (TD) using the Argus/2H system. Our motivations for examining the ECG in the FD were several: 1) a desire to examine pattern recognition parameters in a domain distinctly devoid of preconceived notions of what parameters seem "most reasonable" as shape descriptors; 2) an expectation that information could be obtained in the FD which would be useful in classifying a variety of "problem" waveforms in the TD, e.g. fusion PVCs and noise-contaminated Normal waveforms; and 3) a long-range goal of extending our knowledge of ECG analysis in the FD into the more general context of physiologic signal processing.

We began by computing variable-length Fourier Transforms (FT) on a large variety of waveforms previously analyzed by Argus. From our initial data we learned that: 1) filtering of the ECG was necessary to eliminate troublesome base-line drift which contaminated the lower frequencies of

the ECG power spectrum; 2) the most useful information in terms of ECG waveform classification lay at a frequency band from 2-30 Hz; and 3) the center of gravity (First Spectral Moment (FSM)) of a waveform's power spectrum (normalized so as to eliminate differences in spectral shape for waveforms of similar shape but different amplitude, a common occurrence in Holter recordings) was a fairly stable and accurate QRS shape descriptor, useful as a first-order screen of QRS complexes of truly different shapes.[1]

As our experience with FD analysis of the ECG increased, we made several additional observations including the increased effectiveness of the discriminatory power of FSM if the FT was computed on a 512 msec rather than a 200 msec window (the latter had originally been chosen so as to isolate the QRS complex; the increased window length allowed for the inclusion of the entire PQRST complex). Additional parameters were explored including several "subspectral moments" and a measure of the concentration of a given spectrum's power. Finally, phase information was examined and found to be sufficiently unstable to warrant its exclusion from current analysis strategies.[2]

During the past year we have continued to refine our parameter selections. At present, we are evaluating a correlation-based parameter easily obtained from the FT data utilizing the fact that integration (i.e. correlation) in the TD is equivalent to multiplication in the FD. Initial results suggest that this correlation coefficient is at least as accurate as any TD coefficient currently in use; addionally, it offers the advantage of being easily computable from data already available for use in FD-based feature extraction techniques, thus giving rise to the possibility of a "hybrid" (i.e. feature extraction and correlation) classification algorithm. In particular, TD systems have routinely had to restrict classification approaches to either feature extraction or correlation techniques because the computations associated with each strategy tend to manipulate relatively dissimilar data (e.g. compressed versus raw sample). In the FD however, both features (e.g. FSM) and a correlation measure can be computed from the same data, i.e. the set of coefficients obtained from processing the original signal via the FT. At present we are evaluating the effectiveness of the correlation coefficient as an isolated classification parameter with immediate future plans to generate a hybrid feature/correlation shape-classification algorithm.

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A-12. Performance Evaluation of Ventricular Arrhythmia Detectors

Personnel: R. E. Hermes, BCL
J. R. Cox, Jr., BCL
K. L. Ripley, M.S., Erasmus University

Support: RR 00396

For nearly a decade, providers and users of ventricular arrhythmia detectors have sought a consistent performance evaluation methodology. Now with the advent of the American Heart Association (AHA) Database (A-8), the need is even more pressing. Early work toward establishing such a methodology (PR 11, A-20) was not completed. In recent months, a new emphasis has been placed on the problem and work restarted.

Needed is a performance evaluation methodology which can evaluate systems efficiently, easily, and effectively, as well as providing performance parameters which are consistent and informative. To this end, we have developed a stochastic detector model[1] to which we have applied estimation theory techniques to derive performance parameters. The following block diagram represents the model.

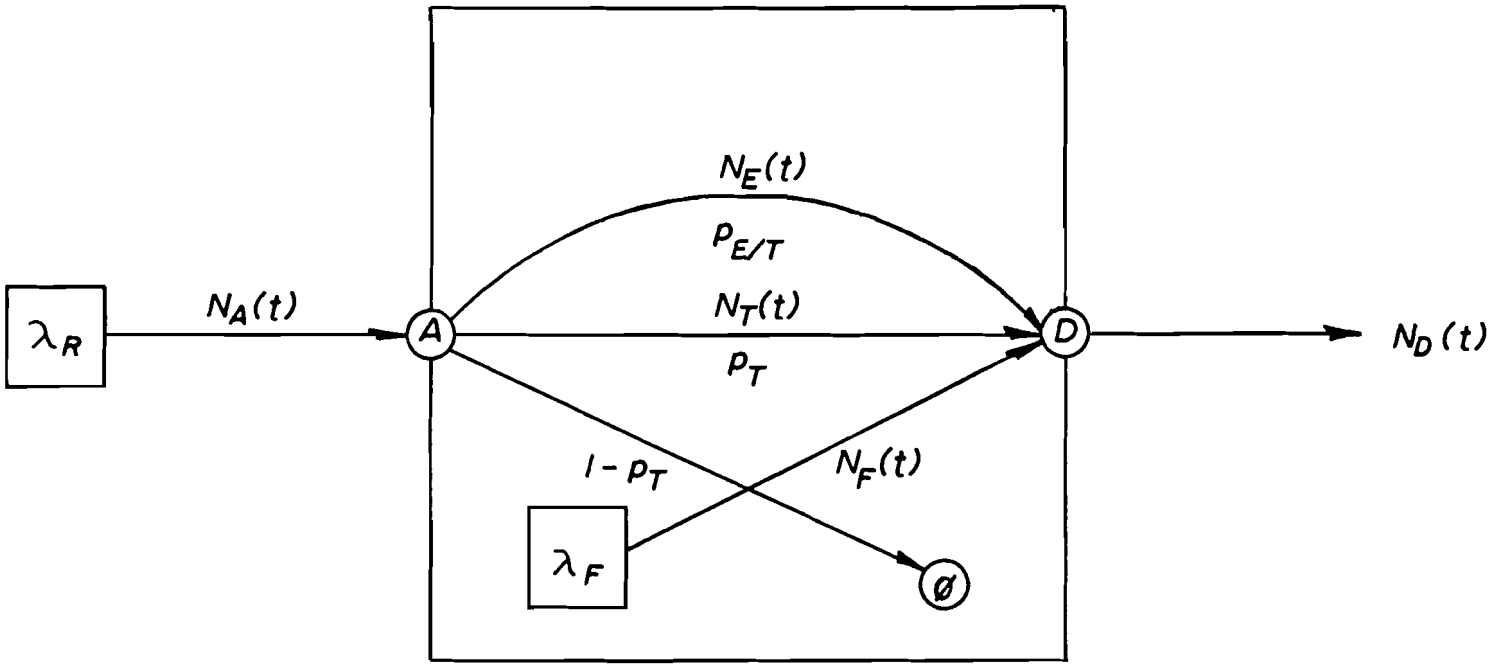
The large block represents the detector and detection process. The detector is presented at Node A with the process $N_A(t)$, which is a string of annotated beats with an arrival rate of λ_R. We realize that a system may do one of three things with an input event; it may detect it with probability p_T, miss it with probability $1-p_T$, or detect it more than once with the conditional probability $p_{E/T}$. In addition to these three possibilities, the detector may also randomly insert a false detection at a rate λ_F. Arriving at node D are the three constituent counting processes, $N_T(t)$, $N_F(t)$, and $N_E(t)$, resulting from correct, false, and extra detections respectively. These processes sum to form the output process $N_D(t)$, which represents all detections. Using these related processes and probabilities, and assuming some probability distributions for correct, false, and extra detections, we have been able to derive, using maximum-likelihood estimation, three parameters to represent system performance. The parameters for correct, false, and extra detections are α, β, and γ.

Preliminary tests using this model have proven successful in providing results with more sensitivity and specificity than present statistical methods. Continuing efforts focus on an even more rigorous mathematical basis for the model as well as proving any assumptions. The model and the resulting model parameters must then be validated.

Concurrent with the model development is work toward a performance methodology. This effort is being coordinated along with plans for distribution and use of the AHA Database (A-8).[1,2] Our hope is that this new evaluation methodology will enhance the use of the database.

$$Pr\,(p_T \leq p) = P_{p_T}(p,q)$$
$$Pr\,(\lambda_F \leq \lambda) = P_{\lambda_F}(\lambda,\beta)$$
$$Pr\,(p_{E/T} \leq p) = P_{p_{E/T}}(p,\gamma)$$

STOCHASTIC
DETECTOR MODEL
(α, β, γ)



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A-13. Modification of Infarct Size

Personnel: R. Roberts, M.D., Medicine
H. D. Ambos, BCL
L. D. Berenbom, M.D., Medicine
W. A. Crafford, M.D., Medicine
R. M. Doroghazi, M.D., Medicine
O. Fukuyama, M.D., Medicine
E. M. Geltman, M.D., Medicine
A. S. Jaffe, M.D., Medicine
J. Markham, BCL
A. T. Marmor, M.D., Medicine
B. E. Sobel, M.D., Medicine
J. L. Vacek, M.D., Medicine
I. R. Weinstein, M.D., Medicine

Support: RR 00396
HL 17646

Studies were performed in the Cardiac Care Unit at Barnes Hospital to assess the effect of selected pharmacological agents on infarct size, ventricular dysrhythmia, and hemodynamics in patients with myocardial infarction. Infarct size was estimated from serial plasma creatine kinase (CK) changes during a 72 hour interval and results in controls were compared to those observed in the treated group. All Holter tapes were digitized and processed by the Argus/H computer system. Hemodynamics including cardiac output were determined by Swan-Ganz thermodilution technique and the effect of the drug assessed by comparing hemodynamics before and after administration. In selected cases left ventricular function was assessed by radionuclide ventriculograms before and after therapy.[1,2,3]

A randomized trial initiated in 1978 to assess the effect of intravenous nitroglycerin on chest pain, ventricular arrhythmias, and infarct size in patients with acute myocardial infarction is progressing well. The intravenous infusion of nitroglycerin is titrated so that the systolic blood pressure does not fall below 100 mm Hg and the heart rate does not increase by more than 10 beats per minute. The drug is initiated immediately after the patient is admitted to the Coronary Care Unit and observed infarct size and ventricular arrhythmias are compared to those of concomitant

randomized controls. Thus far, 134 patients have been entered into the study. Patients have tolerated the drug well without any significant side effects and in patients with cardiac failure or pulmonary edema, marked improvement in hemodynamics has been observed without any significant increase in heart rate.

Nitroglycerin has been shown to be beneficial in animals with experimental myocardial infarction. To determine its effects in man, 134 patients (Class I-II) were randomized to control (C) (n = 62) or treated (T) (n = 72). Nitroglycerin was started at 10 μg/min and increased until a 10% decline in blood pressure, a 10 beats/min increase in heart rate or 200 μg/min was attained. ECGs were recorded continuously and analyzed by the Argus/2H computer system. Frequency of PVCs in the first 12 hours was similar in treated patients and controls (156 $\pm$ 41 (SE) vs 134 $\pm$ 31, NS) as were the incidences of ventricular tachycardia and couplets (4.7 $\pm$ 1.5 vs 2.8 $\pm$ 1.0/12 hours). Infarct size index was similar (11.3 (T) vs 14.6 (C) CK-g-eq, NS). Severity of pain, reflected by the amount of morphine given was similar (13.2 (T) vs 14.6 (C) mg/24 hours). Slightly more lidocaine was required in the treated group averaging (1522 vs 1410 mg/24 hours, NS). Radionuclide ventriculograms showed slight improvement in ejection fraction in the treated group (n = 22) (46 vs 49%, $p<0.05$) versus controls (n = 15, 34 vs 34%) and there was slight reduction of wall-motion abnormalities. Thus, nitroglycerin did not reduce analgesic requirements or ventricular ectopy despite absence of hypotension or tachycardia.

The role of digoxin in the treatment of cardiac failure associated with acute myocardial infarction is controversial. Accordingly, we compared the hemodynamic effects of digoxin to those of dobutamine, an agent with positive inotropic effects and rapid onset of action and clearance ($t_{1/2}$ = 2.5 min) in 6 patients (Killip Class II-III) who were catheterized within 36 hours of acute myocardial infarction. Dobutamine (5 to 10 μg/kg/min) was given intravenously for 30 minutes and then discontinued until hemodynamics returned to baseline. Digoxin (0.0125 mg/kg) was then given intravenously and hemodynamics were recorded for 90 minutes. Dobutamine markedly decreased ventricular filling pressure (23.8 to 8.5 mm Hg, $p<0.05$) and systemic vascular resistance (1624 to 1202 dyne.sec.cm^{-5}, $p<0.05$) and increased cardiac index (2.4 to 3.2 L/min/M^2, $p<0.001$) and stroke work index (23.7 to 35.6 g.m/M^2, $p<0.02$) without eliciting a change in heart rate or arterial pressure. In contrast, digoxin had no effect on filling pressure (19.0 to 18.8), systemic vascular resistance, or stroke work index (21 to 24, $p<0.05$). Neither drug affected the incidence of ventricular arrhythmia. Thus, dobutamine increased cardiac output, decreased filling pressure and afterload as opposed to digoxin which did not affect filling pressure or afterload.

We have previously shown that patients with anterior infarction and inferior infarction have similar infarct size but that the mortality in patients with anterior infarction is 23% compared to only 11% in those with inferior infarction. The patients with inferior infarction exhibited more impairment of right ventricular function compared to patients with anterior infarction with similar infarct size. Thus, we postulated that

inferior myocardial infarction is more frequently associated with right ventricular damage than generally appreciated and that the functional impact of the same overall infarct size is shared by both ventricles. In contrast, in patients with anterior infarction the impact is felt by only one ventricle, namely the left. This hypothesis may in part explain why patients with inferior infarction have a better long-term prognosis. To further test the hypothesis, studies have been initiated with radioventriculography to assess regional ventricular wall motion in right and left ventricles of patients with anterior and inferior infarction. Studies were initiated in 1979. All patients included are admitted to the clinical investigation unit and have ^{99m}Tc-red blood cell ventriculograms performed. Global and inferior and lateral regional right ventricular and left ventricular ejection fractions are measured. Studies have been progressing well and to date 87 patients have been entered into the study. In controls, right ventricular ejection fraction averaged 43 $\pm$ 9 (SD) with variability in repeat studies of 4%. Regional ejection fractions averaged 53 and 79% in inferior and lateral zones. Right ventricular ejection fraction was depressed only early after anterior myocardial infarction (30 $\pm$ 10) but normalized within 10 days (40 $\pm$ 4, $p<0.01$). Inferior and lateral regional right ventricular ejection fraction exhibited comparable sequential changes (Inferior - 26 $\pm$ 7 and 51 $\pm$ 15; Lateral - 17 $\pm$ 16 and 38 $\pm$ 21). In contrast, after inferior myocardial, right ventricular ejection fraction depression, evident at 48 hours (25 $\pm$ 9), persisted (23 $\pm$ 9 and 28 $\pm$ 9 at 10 and 90 days) and correlated with enzymatically estimated infarct size ($r = 0.84$). Regional inferior and lateral values were comparably and persistently depressed. Thus, global and regional right ventricular ejection fractions are depressed only transiently after anterior infarction but are depressed persistently after inferior myocardial infarction suggesting concomitant right ventricular injury.[4,5,6,7]

Treatment designed to protect ischemic myocardium is more effective if administered, as has been shown experimentally, prior to the development of an ischemic episode. This is generally not possible clinically except in those patients who develop recurrent infarction. However, determination of the frequency of recurrent infarction has been difficult as has been prospective identification of subsets of patients at particularly high risk who may benefit most from prophylactic measures designed to protect ischemic myocardium. Based on ST-T changes on the ECG, an apparent incidence of recurrent infarction as high as 86% has been reported. Enzymatic criteria based on total plasma creatine kinase activity, provide an apparent incidence ranging from 35 to 65%, potentially falsely high due to creatine kinase release from non-cardiac sources. Utilization of MB CK isoenzyme analyses may provide increased diagnostic sensitivity and specificity in detection of the initial and subsequent recurrent episode. Thus, a prospective study was initiated in September 1979 involving all patients admitted to the Coronary Care Unit with documented myocardial infarction. The study is designed to determine and characterize the incidence and nature of early recurrent myocardial infarction (extension) based not only on clinical and electrocardiographic criteria but also on analysis of plasma MB CK, plasma myoglobin and serial radioventriculograms and to identify features of patients at particularly high risk. Following transfer from

the Coronary Care Unit, patients are continuously monitored by telemetry for a total of at least 14 days. Clinical and electrocardiographic status are monitored and recorded at least daily throughout the hospitalization. Serial plasma samples are obtained for assay of total CK, MB CK and myoglobin every 4 hours for the first 72 hours and every 12 hours subsequently for 14 days. Re-elevation of MB CK activity to > 15 IU/l after decline of values to baseline or < 8 IU/l are considered evidence of recurrent necrosis. Serial radionuclide ventriculograms are performed initially within 2 days and repeated within 12 days after the onset of initial symptoms. To date, 200 patients have been enrolled. The following is a brief summary of the results: among the 200 patients studied (128 males, 62 females) mean age averaged 68 $\pm$ 17 years. Initial infarction was transmural in 62%, subendocardial in 29% and of undetermined locus in 9%. The overall hospital mortality was 14%. It was 15% among patients with transmural and 12% among patients with subendocardial myocardial infarction. The 165 patients (83%) without early recurrence had an overall hospital mortality of 13.4%. Mortality was 18% for patients with transmural but only 7% for patients with subendocardial infarction. Overall hospital mortality among the 35 patients (17%) who experienced early recurrent infarction was 20%. In the patients with recurrent infarction following an initial transmural infarction overall hospital mortality was 25% compared to 16% in patients with initial subendocardial infarction. Thus, the patients with initial subendocardial and recurrent infarction had an increase in mortality of 128% over that of patients with subendocardial infarction and no recurrence. Among the 58 patients with subendocardial myocardial infarction, 25 (43%) exhibited early recurrent infarction compared to only 8% of those with initial transmural myocardial infarction. Thus, 71% of all recurrences occurred in patients with an initial subendocardial infarction.[8]

Among the 58 patients with subendocardial infarction, 25 (43%) exhibited early recurrent infarction. Identification of such a high risk population has clinical and investigative implications. Patients in this category merit particularly intense and prolonged monitoring for detection of electrocardiographic changes as well as changes in clinical status. Furthermore, they represent a subset of patients in whom the efficacy of therapy can be assessed rapidly and without the necessity for enrolling a prohibitively large number of patients in an extensive trial.

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5. E. M. Geltman, R. Roberts, and B. E. Sobel, "Cardiac Positron Tomography: Current Status and Future Directions," Herz, vol. 5, p. 107, 1980.

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A-14. Ischemic Heart Disease SCOR Computer System

Personnel: J. Markham, BCL
H. D. Ambos, BCL
J. T. Hood, Jr., Radiology
J. A. Johnson, BCL
T. L. Weadon, BCL

Support: RR 00396
HL 17646

Maintenance and operation of the PETT IV tomographic system for cardiac imaging (B-6) continues to be a major activity in this project. During the past year, the programs and operational procedures for processing of the PETT IV scan data were streamlined to make it practical to perform 4 studies a week. The natural history of evolution of jeopardized to infarcted myocardium protrayed by serial PETT IV images is currently under study in order to provide the baseline needed for evaluation of selected treatment regimens on ischemic regions.[1-4]

An interactive tracing system using a joy stick interfaced to the Ramtek display system was designed and built, and will soon be evaluated and tested. A comprehensive software package which will allow non-computer personnel to use the joy stick to outline regions of interest on the Ramtek display will be written during the next year. This system will substantially reduce the time required for procedures such as calculation of infarct size based on analysis of PETT IV images.

Several new programs were written and some of the PETT IV programs were modified so that PETT V data could be processed from animal studies in which the washout of ^{11}C-palmitate from the heart is being investigated. A program was written to compute the average number of counts in selected regions of a set of PETT images. After correction for isotope decay, these data were used to compute decay constants describing the rate of washout of isotope and hence characterize regional myocardial metabolism.

Additional activities of the SCOR Computer System continue to involve analysis of demographic, clinical, laboratory, physiological, and hemodynamic data characterizing patients with acute myocardial infarction, development of an improved, interactive database, characterization of myocardial physical properties based on attenuation and backscatter of ultrasound, and support of clinical and laboratory investigative activities in which enzymatic estimation of infarct size plays a central role.

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A-15. Electrophysiological and Biochemical Factors Underlying the Genesis of Dysrhythmias Due to Myocardial Ischemia and Infarction

Personnel: P. B. Corr, Ph.D., Medicine and Pharmacology
W. A. Crafford, M.D., Medicine
S. R. Phillips, BCL
J. E. Saffitz, M.D., Pathology and Medicine
D. W. Snyder, M.D., Medicine
B. E. Sobel, M.D., Medicine
F. X. Witkowski, M.D., Medicine

Support: RR 00396
HL 17646

During the past year, studies have continued regarding the correlation of electrophysiological derangements and biochemical and adrenergic neural factors underlying malignant dysrhythmia due to ischemia. The overall concept of the research is that potential arrhythmogenic metabolites accumulate in ischemic tissue and exert deleterious effects on membranes and that their effects may be exacerbated by the concomitant influences of the adrenergic nervous system. Thus, the research involves the interaction between potential arrhythmogenic metabolites within ischemic tissue and the influence of adrenergic neural influences on the generation of these metabolites and their overall impact on the profound electrophysiological sequalae apparent in ischemic tissue in vivo. During the last several years we have demonstrated that disparate electrophysiological alterations underlie those dysrhythmias induced by ischemia alone compared to those dysrhythmias induced by reperfusion of the coronary artery.[1] Since both types of dysrhythmias may be collectively important in sudden death in man, each may require different therapeutic interventions. In addition, studies have recently been completed demonstrating a major electrophysiological role of α-adrenergic stimulation during both coronary occlusion and reperfusion.[2] In these studies, α- compared to β-adrenergic input on dysrhythmias induced by left anterior descending (LAD) coronary occlusion and by reperfusion were assessed in chloralose anesthetized cats, a model which has been extensively characterized in our laboratory. As discussed in PR 15, A-15, α-adrenergic blockade with either phentolamine (α_1 and α_2 blocker) or prazosin (α_1 blocker) significantly reduces the number of premature ventricular complexes during coronary reperfusion, abolishes early ventricular fibrillation and prevents the increase in idioventricular rate otherwise seen with coronary reperfusion. Beta-receptor blockade with propranolol is without effect. Ventricular dysrhythmias induced by coronary occlusion alone without reperfusion are also attenuated markedly by α-receptor blockade under conditions in which perfusion (measured with radiolabeled microspheres) within ischemic zones is not affected. In addition pretreatment with 6-hydroxydopamine (to deplete myocardial norepinephrine and render the heart unresponsive to tyramine) attenuates dysrhythmia induced by both coronary occlusion and reperfusion in a fashion identical to that seen with α-receptor blockade. Enhanced α-adrenergic responsiveness is seen during the period of coronary reperfusion as assessed by either efferent left stellate

nerve stimulation or regional infusion of the ischemic zone with methoxamine, a response blocked by α- but not β-blockade. Thus, it appears that during both coronary occlusion alone as well as during subsequent reperfusion, enhanced electrophysiological responsivity occurs to α-adrenergic input and is associated with the induction and the persistence of malignant ventricular dysrhythmia.

More recently, we have completed experiments to assess whether the enhanced α-responsivity characteristic of ischemic tissue was associated with a corresponding increase in α-adrenergic as opposed to β-adrenergic receptors.[3] ^{3}H-prazosin, a specific α_1 receptor ligand, was used to measure B_{max} (total receptor number) and K_D (receptor affinity) in membrane preparations from ischemic and normal regions prior to and at 5 and 30 minutes after coronary occlusion and at 2 and 15 minutes after reperfusion. ^{3}H-prazosin binding was rapid, reversible, saturable and stereospecific. Within 30 minutes after occlusion, B_{max} increased to 178% of control values (to 27 $\pm$ 4 fmol/mg protein, $p<.001$). This increase persisted during early reperfusion but values returned to control 15 minutes after reperfusion (13 $\pm$ 1.6). K_D (2.4 $\pm$ .2) was not significantly altered at any time. Beta-receptor number (^{3}H-DHA binding) and Na^+-K^+ ATPase activity in control and ischemic myocardium 30 minutes after occlusion and 2 minutes after reprefusion were not altered. Thus, the enhanced α-adrenergic responsiveness and marked antiarrhythmic effectiveness of α-adrenergic blockade during ischemia appears to be mediated through a reversible increase in available α-adrenergic receptors. The specificity of the response is indicated also by the apparent lack of alteration of membrane bound enzymes (Na^+-K^+ APTase) and β-receptor number. The time course of altered α-adrenergic receptors correlates well with enhanced electrophysiological responsivity and suggests that one promising approach to the treatment of malignant ventricular dysrhythmias during myocardial ischemia may be blockade of α-adrenergic mediated influences. Additional studies now in progress include verification of α-receptor increases in ischemic tissue with a more purified membrane preparation as well as delineation of the role of amphiphilic metabolites in the receptor alterations.

As reported in PR 15 we have detected the accumulation of lysophosphoglycerides in ischemic myocardium early after myocardial occlusion as well as in effluents from isolated perfused hearts under hypoxic conditions.[4] Studies in vitro in isolated Purkinje fibers and ventricular muscle have indicated that lysophosphatidyl choline (LPC) induces marked electrophysiological alterations closely analogous to those changes characteristic of ischemic tissue in vivo, implicating this amphiphilic metabolite as one potential biochemical mediator of malignant dysrhythmia associated with ischemia.[5] The concept that arrhythmogenesis during early myocardial ischemia is related to the accumulation of metabolites in the hyperfused myocardium is supported by the following observations:[5] 1) the electrophysiological alterations occurring during the first 20 minutes of myocardial ischemia in vivo are reversed when the tissue is superfused in vitro; 2) perfusion of ischemic regions in vivo with saline bubbled in nitrogen results in immediate reversion of the derangements observed in subepicardial action potentials, despite the persistence of hypoxia; 3) arrhythmogenic effects

in vitro have been elicited with venous blood draining ischemic regions in vivo, effects apparently independent of lactate, potassium, pH *per se* and pO_2; and 4) ischemia in vivo is a more arrhythmogenic phenomenon than hypoxia with concomitant, maintained perfusion. More recently, we have demonstrated that LPC increases two-fold in effluents from ischemic feline myocardium in vivo within 10 minutes of coronary occlusion.[6] To determine whether this increase was sufficient to account for arrhythmogenicity of venous effluents, LPC was added to normal feline plasma to yield a comparable increase (0.74 mM), and used to superfuse normoxic endocardium characterized with standard microelectrode procedures.[6] Superfusion with LPC at pH 7.4 induced little change in resting membrane potential (RMP) (-96 ± 1 to -89 ± 3 mV), or amplitude (102 ± 3 to 92 ± 5 mV), although dV/dt of phase 0 (V_{max}) was depressed (178 ± 24 to 62 ± 14 V/sec). In contrast, when pH was reduced to 6.7, marked changes in action potentials occurred with LPC including a decrease in RMP (to 35 ± 7 mV), amplitude (to 36 ± 8 mV), V_{max} (to 26 ± 11 V/sec) and conduction velocity with fractionation of the action potential. Acidosis alone induced only a significant decrease in V_{max}. Thus, the two-fold increase in LPC in effluents coupled with acidosis typical of that seen in ischemic regions in vivo (pH = 6.7) is sufficient to induce marked electrophysiological derangements and may explain the arrhythmogenic properties of venous effluents from ischemic zones. Additional studies have demonstrated that the arrhythmogenic effects of LPC increase 3-fold in the presence of concomitant acidosis (pH = 6.7).[7] Thus, the concomitant effects of acidosis and accumulation of arrhythmogenic metabolites such as lysophosphoglycerides may have profound influences on ventricular dysrhythmia during early ischemia.

Long-chain acyl carnitine accumulates also in ischemic tissue in vivo particularly in the presence of elevated free fatty acid (FFA) and shows striking structural similarities to LPC.[7] In a recently completed series of experiments,[7] we have demonstrated that long-chain acyl carnitine (L-palmitoyl carnitine) induces electrophysiological alterations in canine Purkinje fibers analogous to those seen with LPC. In addition, as with LPC the effects of palmitoyl carnitine were exacerbated by acidosis; the effects of palmitoyl carnitine were additive to those of LPC. Thus, acyl carnitine accumulating during ischemia, coupled with concomitant acidosis and the presence of arrhythmogenic effects of LPC together contribute to the amphiphilic burden of the heart and may be a major precipitant of malignant ventricular dysrhythmia.

More recently, studies have been performed to determine whether alterations in transmembrane potentials induced by LPC depend on actual incorporation of LPC into the membrane. In these studies, canine Purkinje fibers studied with standard microelectrode procedures were incubated with ^{14}C-palmitoyl LPC (200 μmol). After 3 to 6 minutes fibers were rapidly removed from the bath, washed, and extracted for lipid analysis with chloroform: methanol. Lipids were separated by HPLC and individual phospholipids quantified by scintillation spectrometry. Changes in maximum diastolic potential, amplitude and V_{max} occurred only when LPC incorporation was greater than or equal to 0.62 nmol/mg protein. Average incorporation was 1.1 ± .13 nmol/mg representing 2.2 ± 0.2% of membrane phospholipids totaling 50 nmol/mg protein. Thus, marked electrophysiological alterations occur when as little as 2.2% of membrane lipid is supplanted by incorporated LPC.

To determine whether the electrophysiological alterations induced by LPC in vitro resulted in action potentials dependent exclusively on the slow inward current (I_{si}), LPC effects were examined in superfused canine Purkinje fibers with inhibitors of fast (tetrodotoxin) and slow (verapamil or Mn^{++}) channels. As reported in PR 15, LPC induced action potentials dependent exclusively on I_{si} as assessed by their responsivity to blockade by verapamil or Mn^{++} and unresponsiveness to tetrodotoxin.[8] However, experiments by others suggest that I_{si} is exquisitely sensitive to acidosis. Thus under conditions of ischemia with concomitant LPC and acidosis, action potentials dependent exclusively on I_{si} may not be initiated. In an extensive series of experiments we demonstrated that slow response action potentials were propagated despite the presence of concomitant acidosis (pH = 6.7) in both canine Purkinje fibers and ventricular muscle. In addition, slow response action potentials induced by increasing extracellular potassium to 22 mM and addition of isoproterenol were not blocked by concomitant acidosis in either ventricular muscle or Purkinje fibers. Thus, LPC can induce action potentials dependent exclusively on I_{si} in both ventricular muscle and Purkinje fibers independent of concomitant acidosis, suggesting that in the milieu of ischemia action potentials dependent exclusively on I_{si} may propagate reentrant circuits and result in malignant ventricular dysrhythmia.

Since hypothermia may protect the ischemic heart, a preliminary series of experiments has been completed to determine whether hypothermia attenuated the membrane alterations induced by lysophosphoglycerides. At 37° LPC (150 μM) induced marked alterations in the transmembrane action potential including decreased maximum diastolic potential (MDP) (-96 ± 3 to -67 ± 4 mV), amplitude (142 ± 3 to 71 ± 4 mV), dV/dt of phase 0 (V_{max}) (558 ± 22 to 168 ± 4 V/sec), decreased conduction velocity, and fractionation of the action potential. Cooling to either 35° or 33° failed to blunt these deleterious effects. In contrast, cooling to 31° precluded any effects induced by LPC on MDP (96 ± 2 to 98 ± 2 mV), amplitude (140 ± 5 to 134 ± 3 mV) or action potential configuration. V_{max} was changed modestly (396 ± 12 to 252 ± 17 V/sec). LPC effects were not blunted by hypothermia at 29°. Thus, optimal resistance of membranes in ischemic hearts to LPC-induced effects requires hypothermia within a highly specific and narrow range. These results may also indicate the mechanism for the observed protective effect of hypothermia in the ischemic heart and may be related to alterations in phase transition induced by lower temperatures (31°C) possibly preventing the incorporation of LPC and hence its electrophysiological effects on membranes.

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A-16. Characterization of Myocardial Properties by Ultrasonic Parameters

Personnel: J. W. Mimbs, M.D., Medicine
D. Bauwens, M.D., Medicine
R. D. Cohen, M.D., Medicine
J. Markham, BCL
J. G. Miller, BCL
M. O'Donnell, Ph.D., Physics
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 07081
HL 17646
Washington University

The goal of this project is the implementation of a system for ultrasonic reconstruction based on measurements of regional attenuation and backscatter of normal and ischemic myocardium and of normal and atherosclerotic vascular tissue. Although initial experiments have been performed in transmission, the ultimate goal of characterizing tissue will incorporate the

use of reflected ultrasound. The current research program involves experiments designed for investigation of tissue properties utilizing three approaches: 1) characterization of ultrasonic and biochemical properties of tissue in vitro, 2) development of a method for the measurement of quantitative backscatter by reflected ultrasound in vivo, and 3) refinement of a data acquisition system designed by Digisonics to make it applicable to tissue characterization. During the past year a study was completed demonstrating that one of the major determinants of ultrasonic backscatter is intact collagen within regions of infarction, and that the correlation between collagen content and ultrasonic backscatter is close among 110 regions analyzed among 18 dogs studied two, four, and six weeks after coronary occlusion and among hearts from 21 rabbits studied five to seven weeks after coronary occlusion. Demonstration that tissue characterization could be achieved with backscatter analyses provides encouragement regarding the possibility that tissue characterization in vivo will be possible with the use of ultrasound in studies employing reflection as opposed to simply transmission.

Additional studies were completed with isolated perfused rabbit hearts in which it was found that marked alterations in ultrasonic backscatter occur as a function of increased myocardial water content based on results in which the tissue was exposed to selected combinations of media containing buffer, albumin, and hyaluronidase. These changes were independent of those found to be attributable to formed elements in the blood which independently contributed to the magnitude and nature of ultrasonic backscatter. Alterations in ultrasonic properties of rabbit myocardium in animals subjected to administration of Adriamycin to induce cardiomyopathy were identified and quantified, suggesting that ultrasonic tissue characterization may be useful in the early detection of cardiomyopathic processes in vivo as well. In concert, these results indicate that tissue characterization with ultrasound in a fashion ultimately amenable to application in vivo appears to provide useful, quantitative information characterizing myocardium exhibiting selected pathophysiological manifestations.

A-17. Resolution in M-Mode Echocardiograms

Personnel: R. M. Arthur, BCL
R. L. Allen, M.S., Electrical Engineering
T. H. Morrison, B.S., Electrical Engineering

Support: RR 00396
Washington University

Resolution limits of conventional ultrasonic acquisition and display instrumentation were studied both experimentally and via computer simulations. The experimental studies used the digital echocardiograph designed and built at the BCL (PR 15, A-17) for acquisition of ultrasonic echoes along with a TI-980 minicomputer for signal analysis and generation of ultrasonic images. The digital echocardiograph, which combines burst-analog sampling circuitry

and a dual Motorola 6800 microprocessor network, can send 256, 8-bit samples taken every 5 ms to the minicomputer for storage on disk in real time.

The primary limits on resolution come from the transducer and the initial stages of processing. We have studied a 13 mm diameter transducer commonly employed in adult echocardiography (2.25 MHz, unfocused) using both conventional and automatic digital depth compensation to control the gain applied to the transducer output. To determine spatial resolution we used the transducer to scan a static target (AIUM 100 mm test object). Because we know the gain function, both inherent resolution which is fixed by the signal-to-noise ratio of the ultrasonic echoes and the resolution in various display formats (transforms from signals to images) can be determined. Both inherent and display-format resolutions are being studied with the help of Digivision (PR 15, G-9) recently interfaced to the TI-980 minicomputer.

The minicomputer has also been used to simulate the pressure patterns generated by single-element and linear-array transducers. These patterns are plotted in hidden-line perspective views. From the impulse response of a single element convolved with an excitation function we can generate the pressure pattern over an area or the pressure along a line as a function of time. We have simulated point-reflectors in the medium and calculated the received signal at the transducer. This transmit-to-receive simulation capability allows us to determine the minimum separation of two points which can be resolved anywhere in the field of the transducer, as well as the contamination generated by an arbitrarily-located point reflector.

A-18. Interactive Digital Acquisition of Electrocardiograms

Personnel: R. M. Arthur, BCL
E. B. Hagelstein, B.S., Electrical Engineering

Support: RR 00396
Washington University

The development of a microprocessor-based (Intel 8080) cart to perform interactive acquisition of EEGs was previously described (PR 15, A-18). This 8-channel system permits collection of all the signals in either the standard 12-lead or the Frank lead systems simultaneously, while testing for signal quality. It contains a 3-channel, strip chart recorder for waveform output and a self-scan display for presentation of alphanumeric messages to the operator. The operator enters demographic data on the subject and controls the processing sequence through a 16-character keyboard.

Two modifications were made to the hardware during the past year. The floppy disk was replaced as the primary storage medium by an expanded random access memory, which was increased from 12K to 48K bytes. Six seconds

of 8 signals sampled at 500 Hz and 12-bit resolution require a minimum of 36K bytes of memory. The acquisition rate of 6K bytes/sec was at the throughput limit for the disk controller. This constraint limited the testing for signal quality which could be done during acquisition. Further, signal quality analysis and lead calculation from disk files is clearly slower and more complicated than from RAM. The second change was to incorporate the Universal Storage Device (PR 15, G-3) into the cart for permanent storage of the subject file (demographic and ECG data) after all interactive acquisition steps are completed.

The issue of lead calculation has been explored further. Because the typical resistor networks for lead determination in conventional electrocardiographs have been replaced by numbers stored in read-only-memory of our cart, we can easily calculate a variety of leads. We hope to be able to use the cart to study the possibility of individualizing the lead system to the subject, i.e., taking his torso shape into account and to examine the clinical potential of leads, such as the moving electrical center, which give spatial attributes, as well as strengths of cardiac sources.

A-19. Multicenter Post-Infarction Program

Personnel:
G. C. Oliver, M. D., Medicine
L. L. Brandenburger, R.N., Jewish Hospital
K. W. Clark, BCL
J. R. Humphrey, R.N., Jewish Hospital
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
K. A. Madden, BCL
M. A. Marlo, BCL
J. P. Miller, BCL
R. Paine, M.D., St. Luke's Hospital East
S. Thanavaro, M.D., Jewish Hospital
L. J. Thomas, Jr., BCL
P. T. Wallace, Jewish Hospital

Support:
RR 00396
HL 22982
Barnes Hospital
Jewish Hospital
St. Luke's Hospital East

The purpose of the Multicenter Post-Infarction Program (MPIP) was described in detail in last year's progress report (PR 15, A-19). Briefly, ten hospitals in four cities (New York City; Rochester, New York; Tucson, Arizona; and St. Louis, Missouri) have joined together to study patients recovering from myocardial infarction (MI) using a common protocol of data collection. The objective is to study prognostic indicators of sudden death

which will be successful in predicting mortality in other hospitals in this country and perhaps in other countries. The diversity of patient populations, geographic regions, and interests of investigators makes this hope plausible. Each patient is invited to have three special studies: a 24-hour Holter monitor, a low-level treadmill activity test, and a radionuclide angiogram to determine left ventricular ejection fraction. One half the Holter recordings are analyzed at the Biomedical Computer Laboratory (A-4) and the other half at Columbia University.

To date, in St. Louis, 399 patients with documented MI's have been logged in our data collecting system. Of these, 183 were eligible (less than 70 years old, survived hospital stay, and lived in catchment area) and 105 have agreed to participate in the study. Since January 1980, all enrolled patients have had the Holter monitor study and measurement of ejection fraction. Efforts continue to increase the proportion of patients and physicians who agree to the low-level activity test.

A-20. Research Projects Utilizing the Isolated Probe Data Acquisition System

Personnel: B. E. Sobel, M.D., Medicine
H. D. Ambos, BCL
S. R. Bergmann, Ph.D., Medicine
J. O. Eichling, Ph.D., Radiology
S. N. Hack, M.S., Medicine
R. A. Lerch, M.D., Medicine
J. Markham, BCL
M. J. Welch, Ph.D., Radiology

Support: RR 00396
HL 13851
HL 17646

The research in this project is designed to noninvasively quantify myocardial perfusion and metabolism with positron-emitting tracers. Studies are conducted in isolated rabbit hearts (perfused with a solution containing washed sheep erythrocytes) to permit control of many factors that modify myocardial perfusion and metabolism and also in intact dogs, prior to implementation of approaches of proven value in clinical studies.

The development of accurate, quantitative, noninvasive measurements of myocardial metabolism in patients is dependent on thorough characterization of fatty-acid flux in cardiac tissue. Currently we utilize ^{11}C-palmitate as well as a vascular tracer. In addition to monitoring tracer time-activity curves via coincident detection of the positron emission, a number of metabolic functions are being assessed simultaneously. In this manner, ^{11}C-palmitate washout curves can be analyzed in a quantitative manner. Back extrapolation of the monoexponential tail has been found to correlate well

with fatty acid extraction and the slope of the first order function has been found to correlate well with fatty acid oxidation.

In studies completed during the past year, the residual fraction of ^{13}N-labeled ammonia retained by myocardium was studied in isolated perfused rabbit hearts under conditions in which flow and cardiac metabolism were manipulated independently. In 12 hearts perfused with buffer enriched with erythrocytes, residual fraction and half-time of disappearance were not altered despite induction of profound ischemia with a reduction of flow by 75% compared to control flow. This apparently paradoxical phenomenon was explained by enhanced extraction fraction of the tracer due to prolonged residence time. In contrast, under conditions of constant flow in which hearts were exposed to an inhibitor of ammonia metabolism (methionine sulfoximine), retention of ^{13}N radioactivity was reduced by more than 60% and clearance was prolonged despite the absence of any change in flow. These results indicate that retention and clearance of ^{13}N activity by myocardium are influenced considerably by the metabolic status of the tissue and that relationships between retention of tracer and flow are complex, precluding direct estimation of perfusion simply from the amount of tracer sequestered by the heart.

In related studies, the quantitative dependence of myocardial extraction and clearance of ^{201}Tl was evaluated. Although altered cardiac work and oxygenation did not affect kinetics of the process, myocardial extraction increased and clearance became less rapid with decreased flow. These findings suggest that thallium scintigraphy in patients may underestimate ischemia.

To obviate difficulties in quantifying myocardial perfusion with conventional radionuclide methods, studies were undertaken and completed during the past year with the use of positron-emitting radionuclides and isolated perfused hearts. Administration of a tracer selected because of its equal partition in blood and tissue (^{11}C-butanol) was infused in a programmed, exponential fashion, and a derived function reaching steady-state value within several minutes was obtained. The value of the derived function is quantitatively related to perfusion within the tissue. Correlation coefficients between estimates of perfusion and observed perfusion exceeded .93 when appropriate corrections were made for residual radioactivity within the chambers of the heart. The feasibility of employing this approach in vivo was demonstrated with the use of exponential, intravenous infusions of tracer in large experimental animals in whom the radiation burden was well within the limits encountered in clinical diagnostic nuclear medicine. Studies are now in progress to implement and evaluate the quantitative suitability of this approach for measurement of perfusion in vivo, in which detection of the distribution of tracer will be achieved with the use of positron emission transaxial tomography.

Completion of additional studies characterizing the fate of ^{11}C-palmitate administered to isolated perfused hearts indicated that the predominant pool of deposition of isotope was in neural fats within the time frame of the experiments and that the rate of clearance of tracer extracted by the tissue was directly proportional to cardiac work assessed with physiological

parameters and verified by measurement of radiolabeled CO_2 released. These findings facilitated interpretation of positron emission transaxial tomographs obtained in dogs subjected to subcritical coronary stenosis (insufficient to produce infarction but sufficient to impair myocardial metabolism with stress) and in patients with subendocardial myocardial ischemia. Preliminary results obtained in vivo indicate that sequential tomography with ^{11}C-palmitate will localize and sensitively detect myocardium whose metabolism is compromised by transitory ischemia and that delineation of subendocardial infarction as well as the previously documented delineation of transmural myocardial infarction can be accomplished promptly and noninvasively in patients.

A-21. Multicenter Investigation of Limitation of Infarct Size (MILIS)

Personnel: R. Roberts, M.D., Medicine
H. D. Ambos, BCL
D. R. Biello, M.D., Radiology
K. R. Cash, Medicine
K. W. Clark, BCL
E. M. Geltman, M.D., Medicine
R. E. Hitchens, BCL
A. S. Jaffe, M.D., Medicine
K. A. Madden, BCL
C. N. Mead, BCL
J. P. Miller, BCL
D. S. Payne, Medicine
B. A. Siegel, M.D., Radiology
B. E. Sobel, M.D., Medicine
L. J. Thomas, Jr., BCL
A. J. Tiefenbrunn, M.D., Medicine
P. M. Wheelock, Medicine

Support: RR 00396
HV 72941
Washington University

On August 1, 1978 Washington University, in collaboration with four other centers implemented phase II of the collaborative clinical trial of therapy to protect ischemic myocardium. The overall goals of the project include objective evaluation of the efficacy of administration of hyaluronidase and of propranolol in limiting the extent of infarction among patients with acute myocardial infarction and in modifying prognosis. Data are being acquired from five clinical centers, including Washington University, Massachusetts General Hospital, The Medical Center Hospital of Vermont, Parkland Hospital in Dallas, and the Peter Bent Brigham Hospital in Boston. Each of the clinical units is enrolling patients during a three-year interval to provide an overall sample size sufficiently large to statistically test the hypotheses being explored.

In addition to the five clinical units participating in the study, a series of core laboratories is utilized so that uniform objective analysis of data obtained from each unit can be performed in a blinded fashion. These core facilities include a CK Reference Laboratory (at Washington University), a Holter Recording Analysis Reference Laboratory (also at Washington University), an Electrocardiographic Reference Laboratory (at the Peter Bent Brigham Hospital), a Myocardial Infarct Scintigraphy Laboratory (at Parkland Memorial Hospital in Dallas), a Radionuclide Ventricular Function Laboratory (at the Massachusetts General Hospital) and a Pathology Core (at Duke University). Data from each core laboratory are forwarded to the Data Coordinating Center (Research Triangle Institute; North Carolina) so that objectivity in data management and statistical analysis can be assured.

The Washington University components of this project comprise the Clinical Investigation Unit, directed by the Clinical Unit Coordinator, Dr. Allan S. Jaffe, the CK Reference Laboratory, directed by Dr. Robert Roberts, and the Holter Core Reference Laboratory, directed by Dr. Lewis J. Thomas, Jr.

The final protocol, developed after 18 months of planning, defines studies among patients with suspected myocardial infarction identified as early as possible after arrival at each clinical unit and specifically within 18 hours of the onset of acute symptoms leading to admission. The diagnosis of infarction is based on electrocardiographic criteria and clinical indexes, and confirmed with the use of isoenzymatic criteria. Patients to be excluded are those with cardiogenic shock, 75 years of age or older, and those with other significant illnesses or conditions that may affect their response to therapy. Therapy comprising administration of placebo, propranolol, or hyaluronidase is administered in a randomized fashion. For purposes of randomization patients are initially divided into two groups based on the presence or absence of possible contraindications to propranolol. Management of patients participating in the study is standardized by a regimen developed during the planning phases, designed to provide maximum safety to the patient and to avoid potentially conflicting effects of other unnecessary medications. Medical management of each patient remains the responsibility of his own personal physician, and adjunctive emergency measures are, of course, instituted whenever indicated.

A series of endpoints is being utilized to assess the effects of therapy on the extent of infarction and on prognosis. These include enzymatic estimation of infarct size based on analysis of serial changes in plasma MB and total creatine kinase activity, the extent of infarction assessed from the number of electrocardiographic leads in which initial ST-segment elevation is followed by development of criteria of transmural infarction, the distribution and extent of impairment of ventricular function assessed from radionuclide ventriculograms, and the severity and persistence of dysrhythmia assessed from Holter recordings. Additional endpoints include exercise tolerance tests six months after the episode of infarction, ^{99m}Tc-pyrophosphate scintigrams as well as clinical followup recorded on standardized forms developed during the planning phases of the project. Radioventriculograms are obtained three months after infarction, along with a 24-hour Holter

recording. Six months after infarction, myocardial infarct scintigrams are obtained, along with a repeat 35-lead precordial electrographic map and 24-hour Holter recording. A Pathology Core performs studies among patients who expire during the acute or follow-up phases of the study for whom autopsy permission can be obtained.

Since August 1, 1978 eighty-three patients have been entered into the study by the Clinical Investigation Unit at Barnes Hospital. All studies during the acute phase have been completed. Among patients available for follow-up, studies are complete in 87%. A site-visit review by the Policy Board, the Clinical Coordinating Center and the Data Coordinating Center characterized the performances of the Clinical Unit, CK Laboratory and the Holter Laboratory as effective. Over 440 patients have been enrolled by the five centers. The operation of the clinical centers and the core laboratories has been extremely successful. Data-bank analysis studies are in progress. Approval to extend the study through 1983 has been assured.

A-22. Clinical Trial of Nifedipine in Cardioplegia

Personnel: R. E. Clark, M.D., Cardiothoracic Surgery
B. K. Clark, B.S., Cardiothoracic Surgery
K. W. Clark, BCL
G. G. Garcia, Barnes Hospital
K. A. Madden, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 17646
HL 24394

The purpose of this study is to determine the efficacy and safety of the addition of nifedipine, a specific calcium blocking agent, as an adjunct to current cardioplegic solutions used in clinical cardiac surgery. The rationale is to protect against the slow but continual ingress of calcium ion which is in response to the efflux of potassium and ingress of hydrogen ion during ischemia. Immediately upon reperfusion there is a rapid ingress of calcium into the ischemic cell, the explanations for which are not clear. It has been shown experimentally in rabbit and dog hearts that the administration of nifedipine in a perfusate or a cardioplegic solution retards the accumulation of excess calcium in mitochondria and results in less increase in stiffness during the post ischemic-reperfusion phase. Consequently, hearts so treated have greater left ventricular performance than those with cardioplegic solution alone.

The clinical protocol utilizes radionuclide ventriculograms, pyrophosphate scans, CK isoenzyme MB, and 24-hour Holter monitoring in the preoperative phase, the first three postoperative days, and one week and six weeks after operation.

Twenty-four hour Holter recordings are analyzed with the Argus/2H system and reports returned promptly for clinical use. Twenty-five patients have undergone the complete protocol. The data demonstrate two distinctly different patterns. Those patients operated on for coronary artery disease tend to have a high PVC rate in the first three days in comparison to the preoperative recording. By six weeks, the PVC rate is distinctly lower than that observed preoperatively. The data have been highly useful in making judgments with regard to the administration of anti-arrhythmics in the postoperative period. The second group of patients are those with valvular disease who frequently require use of a temporary pacemaker during the first 72 hours postoperatively. The recordings have been difficult to assess because of the large pacemaker spike which with the current program is indistinguishable from a true PVC. We have established that for right-ventricular pacing, a modified Lead III gives high-amplitude pacing artifacts which we believe can be detected reliably. Work is in progress to develop a new high-speed program which will recognize the large and rapid pacemaker discharge and thus analyze for true PVC's only.

The study is to continue for another two years. It is concluded from the early clinical experience that computerized analysis of 24-hour Holter recordings of the electrocardiogram, an important adjunct in the assessment of the efficacy and safety of nifedipine when used in a cardioplegic solution, is of value in post operative clinical management.

B. Quantitative Imaging

Although ultrasound has proven to be a useful source of diagnostic information, results of examinations based on current ultrasonic methods are primarily qualitative and pictorial. To provide quantitative information in addition to a picture, a collaborative effort with the Physics Department has been undertaken to measure regional parameters of tissue. A multiple frequency-attenuation and time-of-flight transmission tomographic reconstruction system has been implemented, and the physical limitations of ultrasonic transmission tomography have been assessed. Improvements in the measurement of the received signal and in processing to correct for beam-width have been made to this system (B-1). The scanner has been used successfully in a series of experimental studies on infarcted dog hearts (B-2). Major improvements have also been made in the software used in simulation studies of geometric acoustics (B-3). An empirical model for anisotropy has been developed (B-4). Estimation of attenuation coefficient with reflected sound has been tested in simulations (B-5).

Stimulated by the clinical impact of the EMI transmission tomographic scanner in 1973, experimental studies were initiated in collaboration with the Division of Radiation Sciences to evaluate the positron coincidence-detection as a method for emission reconstruction tomography. This collaborative activity resulted in a prototype scanner called PETT (Positron-Emission Transaxial Tomograph). A back projection algorithm was implemented in a mini-computer to effect reconstruction from coincidence detections. Extensive studies in patients and animals were conducted subsequently with the PETT III scanner in collaboration with the divisions of Neurology and Cardiology. A subsequent scanner, PETT IV, utilized concepts developed with its predecessor but incorporated a novel technique for the simultaneous collection of four tomographic slices from a single set of detectors. PETT IV is now located in the Cardiac Care Unit for use in the SCOR project for the quantification of regions of myocardial ischemia and infarction (B-6) and for liver studies (B-7). Two new scanners have been developed that permit more rapid data collection and improved spatial resolution. One of these, PETT V, was used in experimental studies in dog hearts (B-8). The newest system, PETT VI, became operational during the summer of 1980 and employs new, fast detectors and an entirely circular motion for rapid data acquisition in neural studies (B-9). One of the most exciting recent possibilities for positron emission tomography results because of new developments in crystal technology and high speed electronics. These now permit the propagation time of each of the two photons created in an annihilation to be measured. Theoretical and experimental studies have been initiated so that a new scanner collecting and using these time of flight measurements can be built (B-10) - (B-13).

Work accomplished during the past year in one of the Laboratory's ongoing projects, that of developing accurate procedures based on fundamental physical principles for computing absorbed dose in clinical radiation-treatment planning, is described in this section. Development of algorithms based on the computation, in three dimensions, of the intensity of Compton scatter and absorption within an inhomogeneous irradiated region has progressed so that consideration of efficient hardware implementation now seems appropriate.

B-1. Ultrasonic Attenuation and Time-of-Flight Tomographic Scanning System

Personnel: G. H. Brandenburger, BCL
J. R. Klepper, BCL
J. G. Miller, BCL
J. G. Mottley, BCL

Support: RR 00396

A. Front-end and processing improvements

Substantial improvement in the estimation of ultrasonic intensity has been realized by time-integrating the received acoustoelectric pulse. Formerly the ultrasonic intensity was estimated from the peak of the pulse as measured with an analog peak detector. Propagation of an ultrasonic pulse through an inhomogeneous refracting medium gives rise to phase-cancellation error in piezoelectric receiving transducers of wide aperture[1] (PR 14, B-1; PR 15, B-1) while the acoustoelectric received pulse is only stretched in time due to the inhomogeneity. Thus the peak of the acoustoelectric pulse is less reliable for estimation of attenuation when the medium is refracting while the time-integral of the received pulse remains the same. An analog integrator was applied to the acoustoelectric pulse and was demonstrated to yield more reliable estimates of attenuation, particularly for propagation through edges of refracting media.

A method was developed for improving the accuracy of the slope of attenuation from measurements made with a focused transmitting transducer.[1] Significant improvement in spatial resolution has been achieved with the use of a focused transmitting transducer instead of a planar transducer of comparable aperture (PR 15, B-1). However, the diameter of the transmitted beam in the focal region did exhibit a dependence which is approximately inversely-proportional to the ultrasonic frequency. As a result, the region of tissue subtended by the transmitted beam varies with ultrasonic frequency. The computation of the slope of attenuation was predicated on the assumption that the same region of tissue is insonified at each frequency. Hence, the slope computation will be compromised, particularly near edges within the object.

Figure 1 demonstrates the error in the slope for a homogeneous cylinder of laboratory gelatin which approximates the properties of tissue. A 1.2-cm aperture, 10-cm focal-length transmitter was used. Panel a) is the reconstruction of the gelatin cylinder from attenuation measurements at 3 MHz. Substantial error due to reflection loss at impedance discontinuities is evident both in the ring artifact in the image and in the corrupted values of attenuation reconstructed throughout the object. Panel b) is the reconstruction of the slope of attenuation, computed from measurements between 3 and 6.5 MHz. The ring artifacts

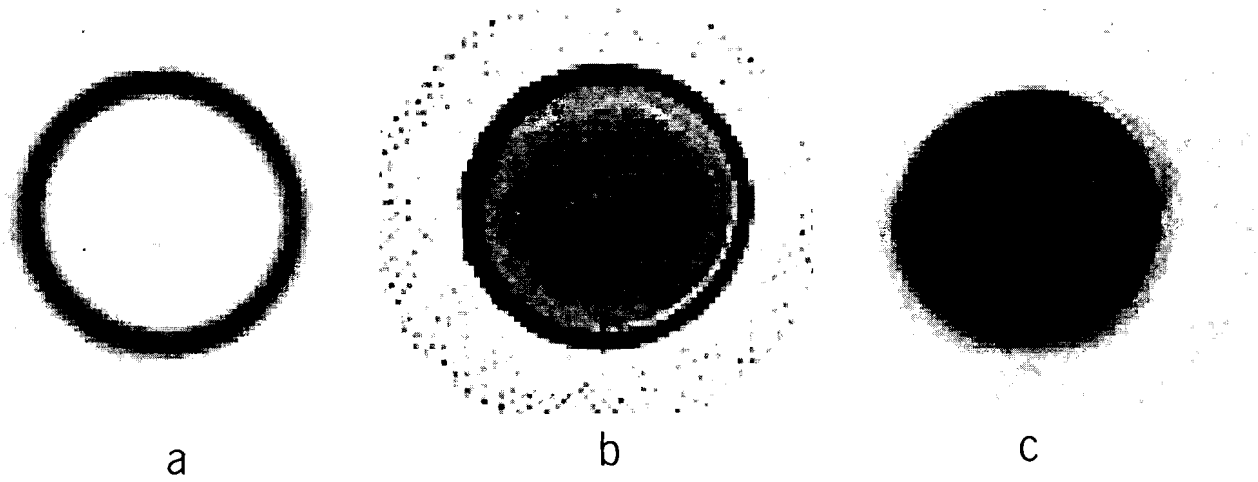
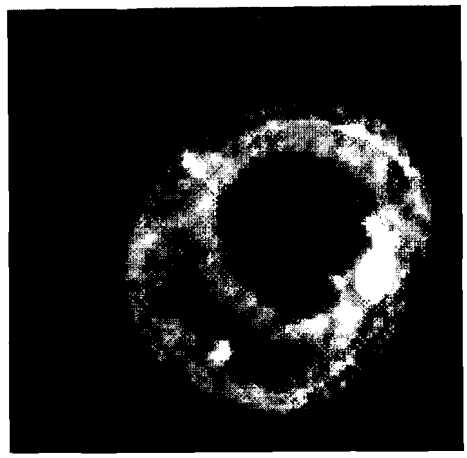


Figure 1. A comparison of reconstruction methods for attenuation measured in a homogeneous cylinder of tissue-like laboratory gelatin:

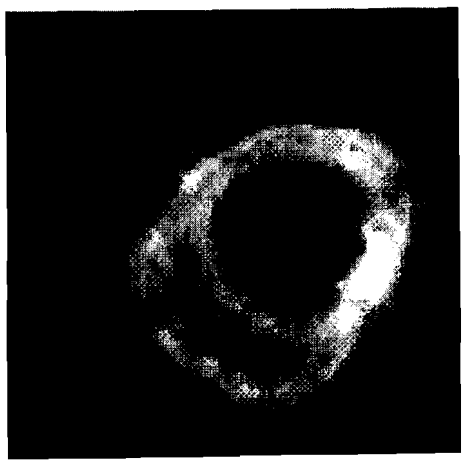
Panel a) attenuation measured at 3 MHz.
Panel b) slope of attenuation (uncompensated).
Panel c) slope of attenuation compensated for the variation of the transmitted beamwidth with frequency.

in the slope image appear to be due to the inconsistencies resulting from beamwidth variation with frequency. Panel c) is a reconstruction of the slope after the individual projections at each frequency were spatially filtered[1] to correct for the beamwidth frequency dependence. The edge artifact is almost completely removed and the reconstructed slope values are consistent throughout the cylinder.

We demonstrate further, with a tissue sample, the importance of correcting for beamwidth variation with frequency. Figure 2 is a comparison of corrected and uncorrected slope reconstructions of an intact dog heart. Black corresponds to zero attenuation and white represents 0.24 $cm^{-1}MHz^{-1}$ slope. The region of infarct (details of the tissue preparation and pathology appear in B-2) is clearly visible in both images. We note, however, that some apparently false detail appears in the uncompensated reconstruction in Panel a). In particular, several apparently highly attenuating objects are visible which are not apparent in the beamwidth compensated reconstruction of Panel b) in which the infarct is still clearly resolved.



a)



b)

Figure 2. A comparison of beamwidth compensated and uncompensated slope reconstructions of a dog heart containing a single myocardial infarct at 3 to 4 o'clock.

Panel a) is the uncompensated reconstruction.
Panel b) was compensated for the variation of the beamwidth with frequency. Beamwidth compensation reduces edge artifacts with little apparent sacrifice in spatial resolution.

B. System enhancements

Numerous improvements to the CUTARSYS (PR 13, B-3) software were incorporated:

1) The time-of-flight data-acquisition algorithm was modified to improve edge recognition accuracy and to permit measurements using tone-bursts for up to 8 frequencies. Results of the time-of-flight measurements for dog heart appear in (B-2).

2) The projection-moments software was rewritten and extended for use in the anisotropy study (B-4).

3) The ability to print and display the difference between reconstructed images was added. This is useful in studies of the frequency-dependent indices such as the slope of attenuation and was used in the work on beamwidth frequency-dependence.

4) Software was written to generate spatial filters based upon independent beamwidth measurements and a Gaussian beam-profile model. The resulting filters were used in conjunction with a modification of the software for spatial filtering of projections to implement the correction for beamwidth frequency dependence.

5) The CUTARSYS software was expanded for conversion of image and projection data from external sources such as the Universal Storage Device (G-3). Data produced at the Laboratory for Ultrasonics, Department of Physics, were brought into CUTARSYS for image display and hardcopy, and for tomographic reconstruction.

1. J. R. Klepper, G. H. Brandenburger, J. W. Mimbs, B. E. Sobel, and J. G. Miller, "Application of Phase Insensitive Detection and Frequency Dependent Measurements to Computed Ultrasonic Attenuation Tomography," IEEE Transactions on Biomedical Engineering, in press.

B-2. Ultrasonic Computed Tomography of Experimental Infarct in In-Vitro Dog Myocardium

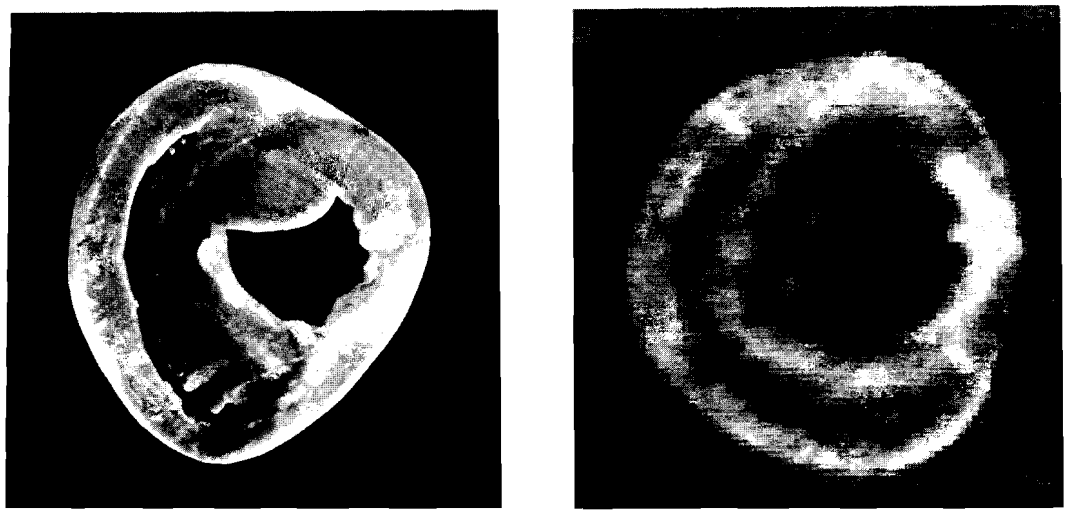
Personnel: G. H. Brandenburger, BCL
J. R. Klepper, BCL
J. G. Miller, BCL
J. W. Mimbs, M.D., Medicine
J. G. Mottley, BCL
M. O'Donnell, Ph.D., Physics
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 17646

Myocardial infarct in the dog was selected as a model to test the hypothesis that pathologic changes in tissue are accompanied by changes in the ultrasonic attenuation or speed of sound in that tissue. Accordingly, three dogs were studied in vitro 7 to 9 months after coronary artery ligation. Although the techniques described in this report cannot be applied directly to the examination of the heart in vivo, the demonstration that such techniques can be successful in transmission ultrasonic imaging in vitro may provide information that is useful in the eventual application of quantitative imaging techniques to imaging in vivo using reflected ultrasound.

Previous studies from this laboratory have demonstrated that the principal artifact in ultrasonic imaging based on attenuation results from phase cancellation artifacts exhibited by piezoelectric receiving transducers (PR 14, B-1). Consequently, measurements were made using a phase insensitive acoustoelectric receiving transducer. An example of an attenuation-based reconstruction from such measurements is given in Figure 1. An optical photograph of the approximate plane imaged is shown in panel a) and a reconstruction from data taken at 5.1 MHz is shown in panel b). The infarct is visible as the white mass on the right hand side of the optical photograph and clearly correlates with the white region of the reconstructed acoustic image of the plane in panel b). The reconstruction is windowed such that black corresponds to zero attenuation and white corresponds to 1.1 cm^{-1}. The location and size of this nearly transmural infarct make it easily detectable with a narrowband reconstruction based on the apparent attenuation.

The location and size of the infarct were traced through several image planes of this heart. Figure 2 shows four images of this heart in planes separated by approximately 1 cm. The infarct is clearly visible in the reconstructions of panels b) and c) and appears to be getting successively smaller in planes approaching the apex. No discernible infarct appears in the reconstruction of panel d) which corresponds to a region approximately 1 cm from the apex. Optical examination of this region of the heart after ultrasonic scanning also revealed no



a b

Figure 1. Cross-sectional images of a dog heart containing a myocardial infarct. Panel a) is an optical photograph of the approximate plane imaged in the reconstruction in panel b). The reconstruction is based on measurements of attenuation at 5.1 MHz. White represents high attenuation, and dark represents low.

apparent infarct. A comparison of time-of-flight and attenuation images of the same plane is shown in Figure 3. The infarct is clearly visible in the time-of-flight scan.

Although the images shown in Figures 1, 2, and 3 delineate the zone of infarct, the resulting quantitative estimates of attenuation are substantially in error. Reconstructed images at a single frequency are not always adequate to identify the zone of infarct. In particular, geometry-dependent reflection losses which compromise the quantitative estimates of the attenuation at a single frequency may be so severe as to obscure the zone of infarct. Reconstructions from data taken at 3 and 5 MHz on the second heart are shown in Figures 4a and 4b, respectively. The infarct is barely noticeable in the 3 MHz reconstruction in Figure 4a since the edge artifacts in this reconstruction are equal to or greater than the reconstructed values of the attenuation within the infarct. The infarct is less obscure in the 5 MHz reconstruction of Figure 4b because the increased attenuation at 5 MHz constitutes a larger component of the measurement while the frequency independent reflection loss errors remain approximately constant. However, severe artifacts are still prominent in the 5 MHz reconstruction.

The reconstruction of the slope of the attenuation coefficient computed over a range of frequencies is expected to be better than the reconstructions made directly from any of the individual narrowband measurements. The slope of attenuation, computed from the same data set used to create the images in Figure 4, is reconstructed in Figure 5. The slope was estimated from measurements of attenuation over the range 3 to 5 MHz using beamwidth compensation (B-1). An optical photograph of the approximate cross-section of heart images is shown in panel a). The subendocardial infarct is the region of white scar located in the posterior region of the heart.

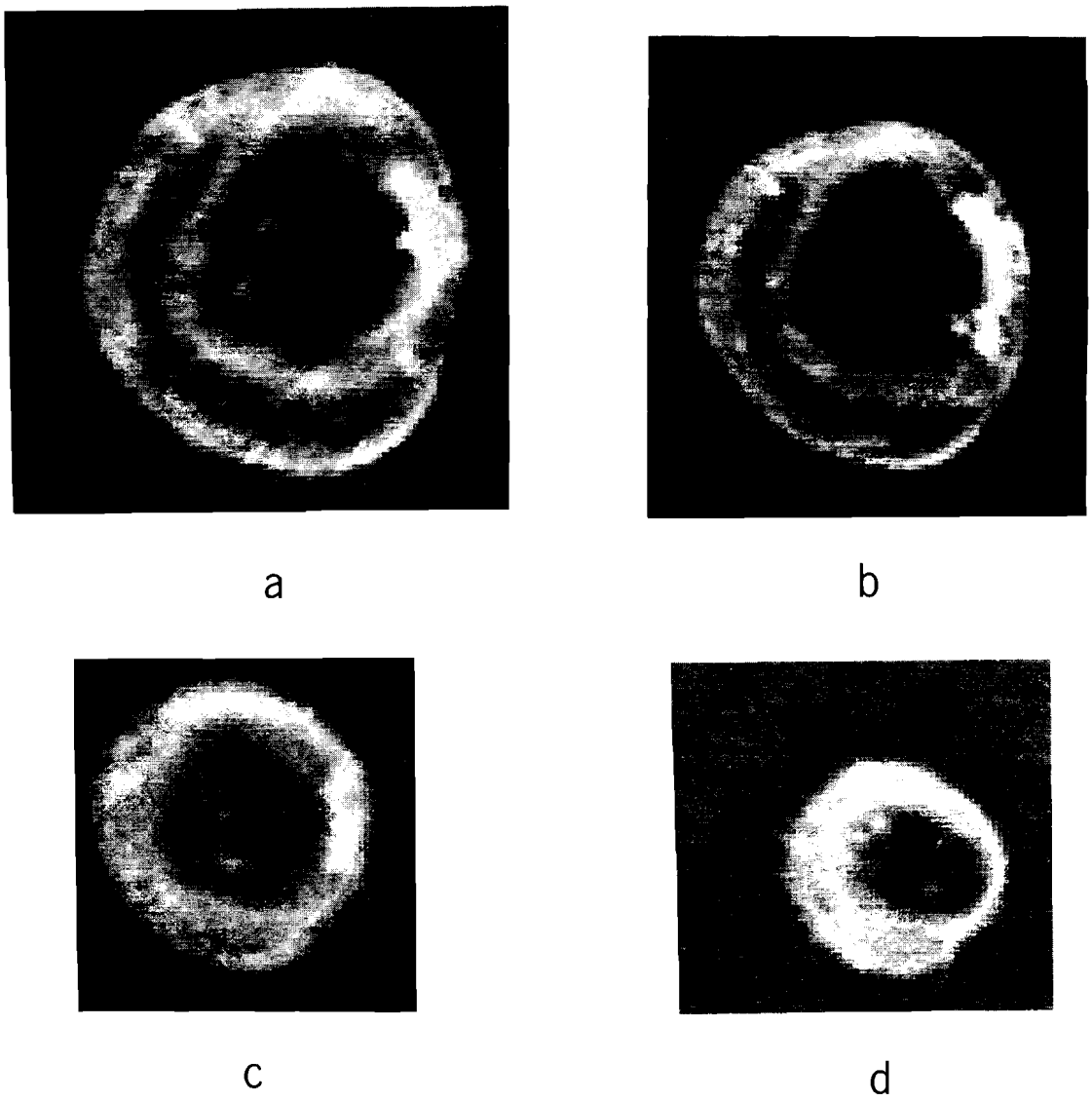
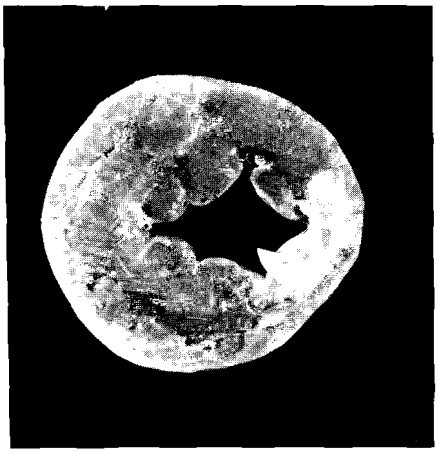
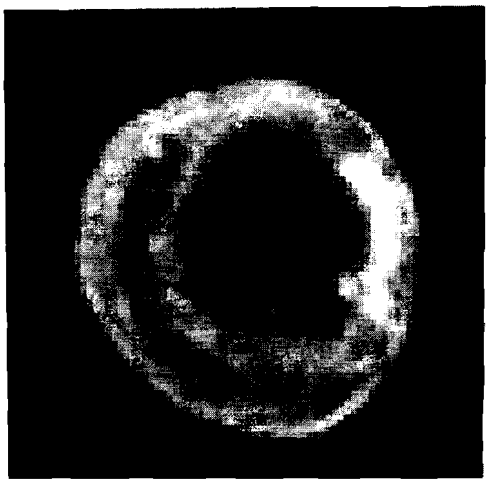


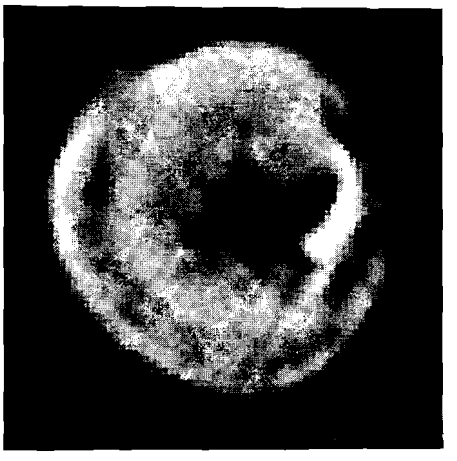
Figure 2. Reconstructed images of a dog heart containing a myocardial infarct from attenuation measurements at 5.1 MHz. Panel a) is the same reconstruction as shown in Figure 1. Panels b), c), and d) are planes parallel to the image plane shown in panel a) with each being 1 cm closer to the apex of the heart.



a

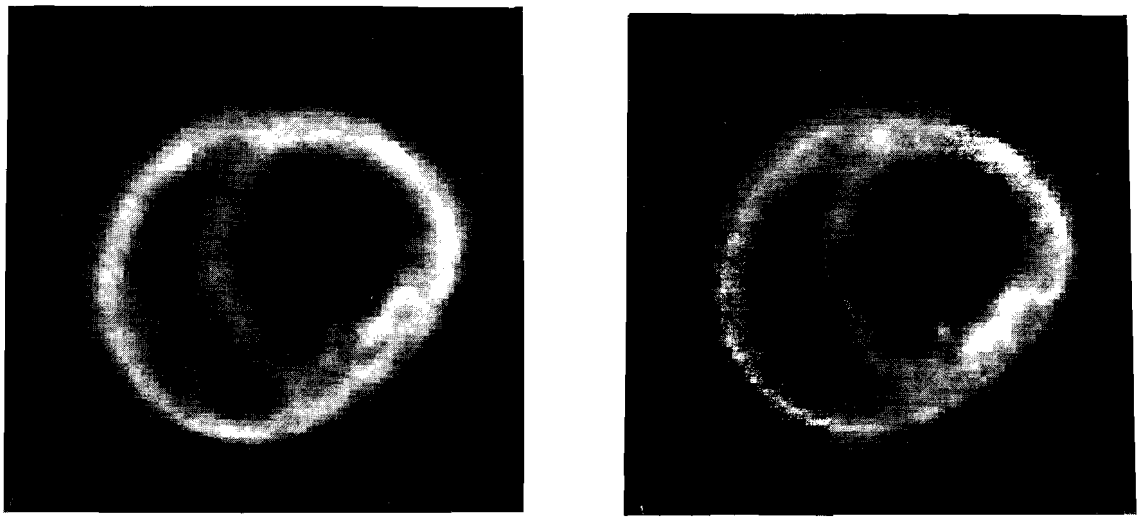


b



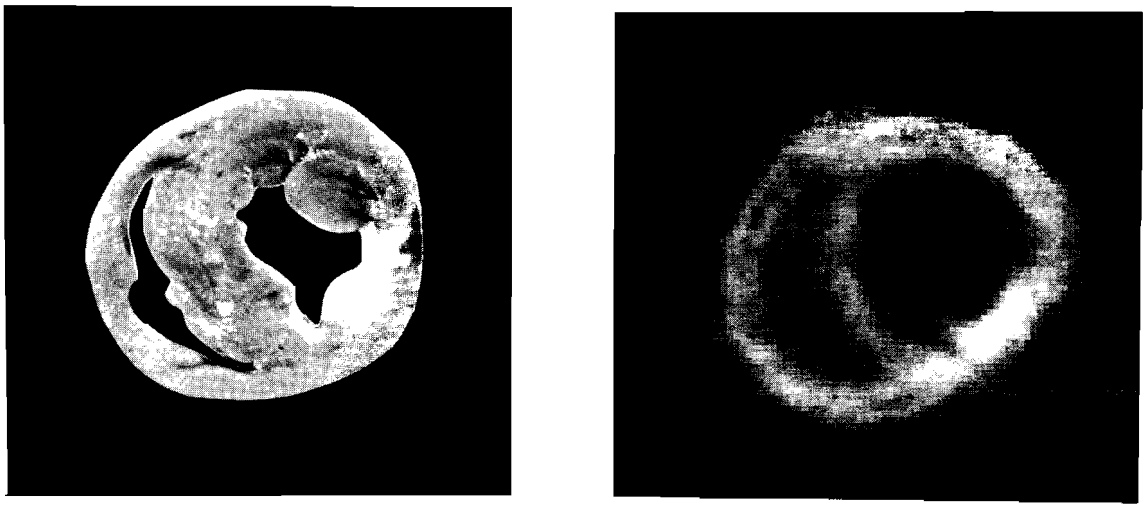
c

Figure 3. A comparison of time-of-flight and attenuation images of the same image plane of a dog heart containing a myocardial infarct. Panel a) is an optical photograph of the approximate cross-section imaged. Panel b) is a tomogram from attenuation measured at 5.1 MHz. Panel c) is a time-of-flight image of the same plane with white representing high speed of sound; dark represents low.



a) b)

Figure 4. Reconstructions of a dog heart containing a myocardial infarct. The images were reconstructed from attenuation measured at 3 MHz (panel a) and 5 MHz (panel b).



a b

Figure 5. Cross-sectional images of a dog heart containing a myocardial infarct. Panel a) is an optical photograph of the approximate image plane shown in the image in panel b). The image was reconstructed from the slope of attenuation from 3 to 5 MHz; white represents high slope of attenuation; dark represents low. The improvement in the resolution of the region of infarct is shown by comparison with the single-frequency attenuation images of the same plane in Figure 4.

B-3. Modeling and Simulation of Ultrasonic Wave Propagation in the Context of Ultrasonic Imaging

Personnel: G. H. Brandenburger, BCL
J. R. Cox, Jr., BCL

Support: RR 00396
Washington University

A. Simulation software development

The basic framework of the geometrical acoustics simulation software system was completed. As a subsystem within CUTARSYS (B-1; PR 15, B-1), the simulation shares all the processing, reconstruction, spatial filtering, imaging, graphics, and file-access capabilities of CUTARSYS. Improvements include:

1) A 10-fold increase in speed reduced the time required for ray tracing from the typical 24 hours to 2.4 hours.

2) Each transmitted beam can now be sampled with up to 100 rays (instead of 10), as required for more accurate characterization of the beam. This allows the simulation of the beam profile at the receiver and holds promise for use in the study of transmitted beam characterization at the receiver by spatial moments of the intensity. The corresponding modifications to the ray summing software (PR 15, B-2) for 100 rays are partially completed.

3) Ray tracing is now restartable, permitting recovery from machine failure during long runs, and has been enhanced with a command monitor. The monitor is useful in the development of new software owing to the ability to enable and disable the exhaustive diagnostic listing features at any point in a simulation. Without these features diagnosis of simulation or program errors which occur hours into a run can be difficult.

Figure 1 demonstrates some of the important effects modeled by the system. All images are tomographic reconstructions of attenuation-based parameters in a simulated dog-heart geometry. Panels a) and b) represent simulations assuming a circular-aperture piezoelectric receiving transducer. Panels c) and d) are the corresponding simulations for an acoustoelectric receiving transducer free of phase-cancellation error (PR 15, B-1, B-2). The simulated object has a refractive index 5% different from the surrounding medium. Panels a) and c) represent measurements of attenuation at a single frequency (3 MHz) and demonstrate significant error near edges due to reflection losses. The slope of attenuation over 3 to 6.5 MHz is reconstructed in panels b) and d). While the reconstruction of phase insensitive measurements in panel d) exhibits considerable improvement over panel c), the image corrupted by phase-cancellation in panel b) is only marginally improved. Panel e) is a reconstruction

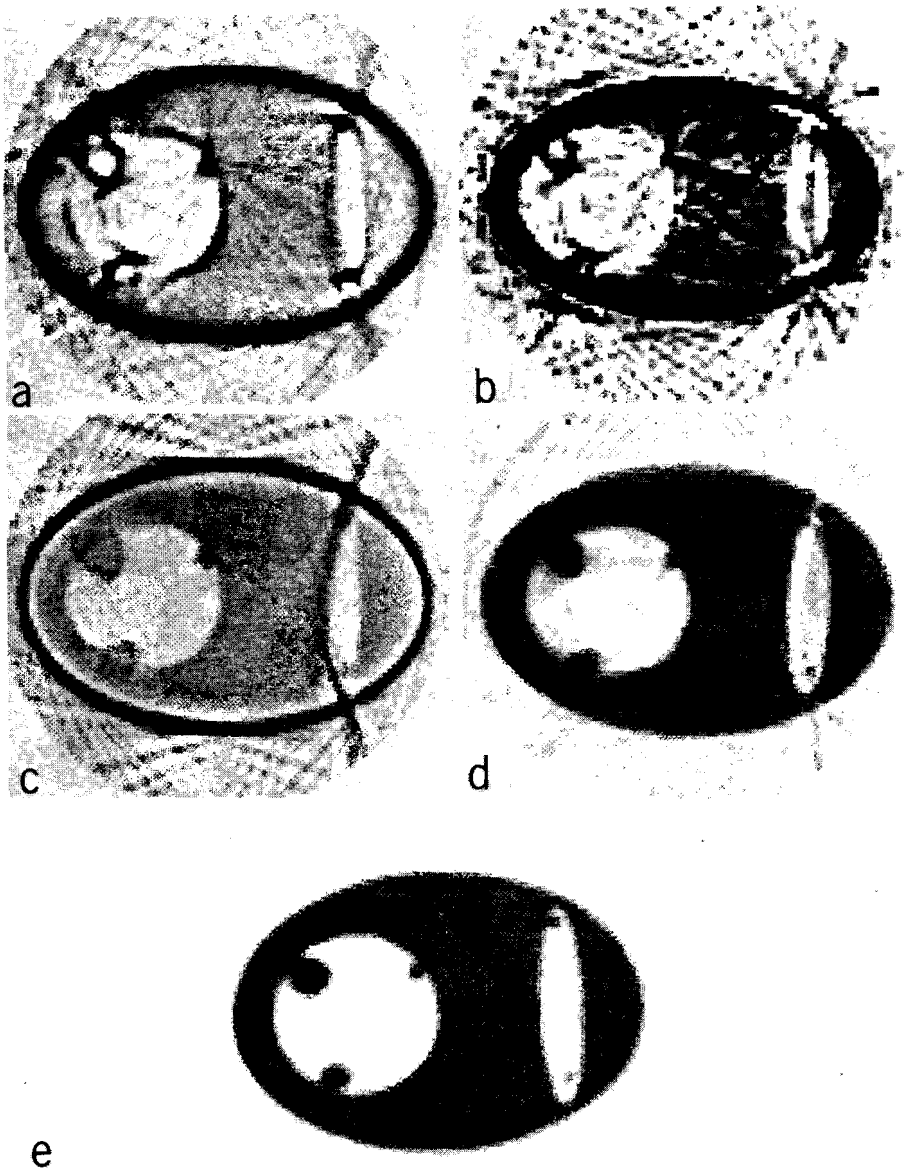


Figure 1. Simulated dog hearts showing effects of refraction and phase cancellation in a single-element wide aperture piezoelectric receiving transducer. Panels a) and b) are reconstructions of data simulating measurements of the piezoelectric receiver. Panels c) and d) represent comparable reconstructions of data simulating an acoustoelectric receiving transducer. Panels a) and c) were reconstructed from simulated measurements made at 3 MHz. Panels b) and d) were reconstructed from the slope of attenuation over 3 to 6.5 MHz and exhibit reduced artifact due to reduction of error from reflection. The acoustoelectric measurements do not exhibit phase-cancellation error, and corroborate results of actual measurements that indicate that phase-cancellation is the predominant error source in transmission attenuation tomography.

of an identical object free of error due to non-unity refractive index. These results are in qualitative agreement with actual observations in the laboratory.

A new simulation software package was developed for research into the effects of anisotropy on tomographic reconstruction. This effort was an outgrowth of earlier work and results are detailed in (B-4). Besides directly simulating a wide range of geometries, the software also can be used to modify ray-tracing based simulations of linearly-directed anisotropy (B-4). The experience gained during this development suggests methods for a number extensions to the ray-tracing algorithms, including: a) inclusion of both linearly and tangentially-directed anisotropy; and b) accommodation of a wider range of object geometries.

B. Theory of geometric acoustics

The literatures of geometric optics, and its mechanical-wave counterpart, geometrical acoustics, have been reviewed. The primary goals of this effort were:

1) More detailed modeling of the specularly reflected, refracted, and diffracted components of a particular pulse-wavefront impinging a surface of refractive-index discontinuity;

2) A detailed geometrical acoustics model for a focused transmitting aperture;

3) Extension of the transmission measurement simulation model to reflection measurements;

4) An accurate model for time-of-flight measurements;

5) An extension of the existing finite pulse-duration model, presently used in the ray-tracing, which will also include dispersive effects; and

6) A geometrical acoustics (ray) model for media exhibiting anisotropic acoustic velocity. None appears to exist at this writing.

The outcome of this study will be the identification and/or derivation of a series of models to be applied in the ongoing development of the ray-tracing simulation. While the study is far from complete, we have already compiled a number of potential refinements to the existing ray-model which include:

1) A more detailed model of reflection at a boundary has been identified which accounts for lateral displacement of the beam and yields more exact representation of the change in phase.[1]

2) The classical geometrical acoustics/optics model does not account for the diffracted energy components radiating from discontinuities in the first-derivative of the refractive index (edges). The Geometrical Theory of Diffraction (GTD), which has evolved over the last 25 years, partially overcomes this discrepancy. Despite its being a theory which has defied formal proof, GTD has been applied successfully to a broad range of problems formerly too complicated for analytical solution, but of geometry close enough to a wavelength to preclude description by classical ray optics. GTD has apparently not been applied to the modeling of the acoustics associated with imaging. We have identified methods via GTD, for extending our ray-model to include the effects of diffraction.

3) A two-part model has been proposed to simulate the transmitted beam of a focused aperture. The first part is a refinement of the existing focused-beam simulation (PR 15, B-2) which permits more accurate representation of the central lobe of the beam given a description of the transmitter aperture, apodization, geometry, and refractive index. Part two augments the beam representation with diffracted rays (analogous to those of GTD) whose properties are derived from the evaluation of the diffraction integral for the aperture. The diffracted rays describe the side lobes of the beam and permit more accurate modeling of a transmitted pulse beyond the initial wavefront described by classical ray-optics.

The simulation methodology under development appears to be feasible. The detailed simulation of the received wavefronts, for both transmission and reflection in anisotropic inhomogeneous media, would be important for the design of quantitative clinical ultrasonic imaging methods for tissue for the following reasons:

1) Simulation provides a means for evaluating the performance of new imaging methods, with the important capability of varying specific test parameters with a degree of control not feasible in test phantoms.

2) New models can be tested and refined through the simulation by comparisons with laboratory measurements.

3) Algorithms developed for simulation may also find direct application in imaging systems. At the very least, the understanding gained in developing accurate models of ultrasonic wave propagation should be helpful in the development of approaches to quantitative imaging.

1. J. R. Klepper, G. H. Brandenburger, J. W. Mimbs, B. E. Sobel, and J. G. Miller, "Application of Phase Insensitive Detection and Frequency Dependent Measurements to Computed Ultrasonic Attenuation Tomography," IEEE Transactions on Biomedical Engineering, in press.

B-4. Anisotropy in Ultrasonic Attenuation and Its Implications for Computed Transmission Tomography

Personnel: G. H. Brandenburger, BCL
J. R. Klepper, BCL
J. G. Miller, BCL
J. G. Mottley, BCL
D. L. Snyder, BCL

Support: RR 00396

Ultrasonic parameters such as attenuation and scattering have been shown to be strong functions of the direction of wave propagation relative to an intrinsic direction within various materials. Muscle tissue and certain metals and crystals can possess strongly anisotropic components of attenuation, acoustic velocity and scattering. Anisotropic attenuation and scattering in tissue are reported in the literature primarily as pairs of measurements made with orthogonal propagation paths. The functional dependence of attenuation on angle does not appear to have been characterized for most biological tissue. Similarly, the frequency dependence of the anisotropy itself is a largely unexplored but potentially useful tissue characterization parameter. The effects on various ultrasonic imaging methods of the angular dependence of the parameter being imaged appears to be another important field awaiting investigation.

We developed a model for anisotropy as a continuous function of angle of propagation. This model was then fit to an empirical angular dependence function for the slope of attenuation in myocardium (Figure 1). The effect of this anisotropy on filtered back-projection tomographic reconstruction was analytically derived for simple geometries using the model. Effects of anisotropy were further demonstrated for various elliptical geometries by computed tomographic reconstruction of simulated data.

I. An Empirical Anisotropy Model

We denote the parameter of interest by $\alpha(x,y,\psi)$; its anisotropic character within a volume element dxdydz is modeled as

$$\alpha(x,y,\psi) = \alpha_o(x,y)(1 + C(\psi)), \qquad (1)$$

where $\alpha_o(x,y)$ is an intrinsic isotropic component, ψ is the angle between the volume element's anisotropy axis and the direction of wave propagation, and $C(\psi)$ is the anisotropic angular dependence function. On the basis of measurements from myocardium, the angular dependence is assumed to have the form

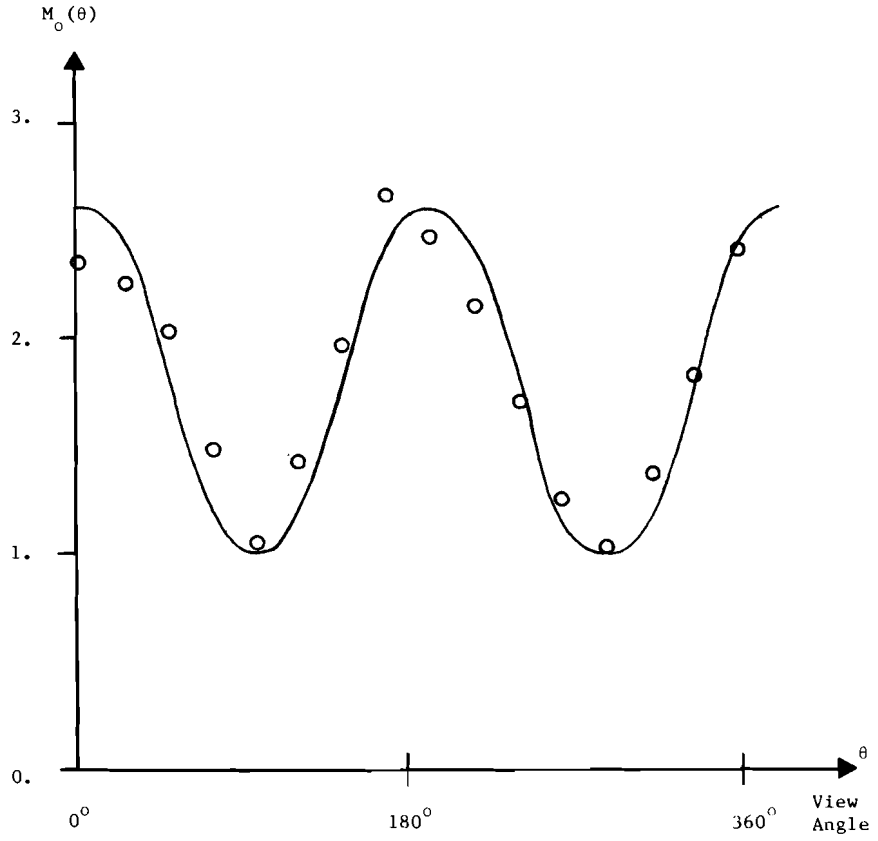


Figure 1. The zero-order moment $M_o(\theta)$ of the slope of the attenuation is plotted against angle over 360 degrees. Moments were computed from measurements of the slope in an isolated section of dog left ventricle. The ordinate is scaled such that the smallest moment has the value 1.0; the maximum value attained represents the anisotropy ratio for this sample, approximately 2.6:1.

$$C(\psi) = \beta \cos^2(\psi) \qquad (2)$$

where $\psi = 0$ is the direction of the largest ultrasonic attenuation (along the muscle fibers).

II. Tomographic Reconstruction of Anisotropic Projections

Images of tissue have been reconstructed from ultrasonic attenuation measurements using filtered back-projection algorithms and iterative algebraic algorithms. The effects of anisotropy on tomographic reconstruction are investigated here in the context of filtered back projection for the following reasons:

a) Filtered back projection can be expressed analytically, thus permitting the expression of anisotropic effects in closed form for simple geometries.

b) Conclusions about the effects of anisotropy on tomography, based upon models and simulations presented here, can be compared with results for reconstructions of tissue from this and other laboratories.

The projections for an annulus were analytically derived for both linearly-directed and circumferential anisotropies (Figure 2). The resulting filtered back projection reconstructions were then derived analytically for the linearly directed case and were in excellent agreement with computer reconstructions of the analytically derived anisotropic projections. The effects of anisotropy for more complicated geometries were demonstrated by computer simulations.

Figure 3 is a schematic diagram of the superimposed circle-and-ellipse geometry to be simulated. All circles possess an isotropic attenuation of 0.5. The two ellipses are characterized by a linearly directed anisotropy parallel to the lines shown. Each ellipse has an isotropic component of attenuation of 0.5, equal to the surrounding disks. The 2:1 anisotropy magnitude used for the ellipses causes the attenuation measured parallel to the lines shown to appear twice as large as measured normal to the lines.

In Figure 4 an ellipse is reconstructed which illustrates the potential effects on regions neighboring the anisotropic ellipse. The substantial positive and negative errors surrounding the ellipse are expressed as a percentage of the value reconstructed within the ellipse. Objects adjacent to the long sides of the ellipse will reconstruct with underestimated attenuation values due to the negative errors on either side of the ellipse. Near the ends of the ellipse objects will reconstruct with overestimated attenuation values.

In panel a) of Figure 5 the entire collection of objects (anisotropic ellipses and isotropic disks) are reconstructed to illustrate the effects

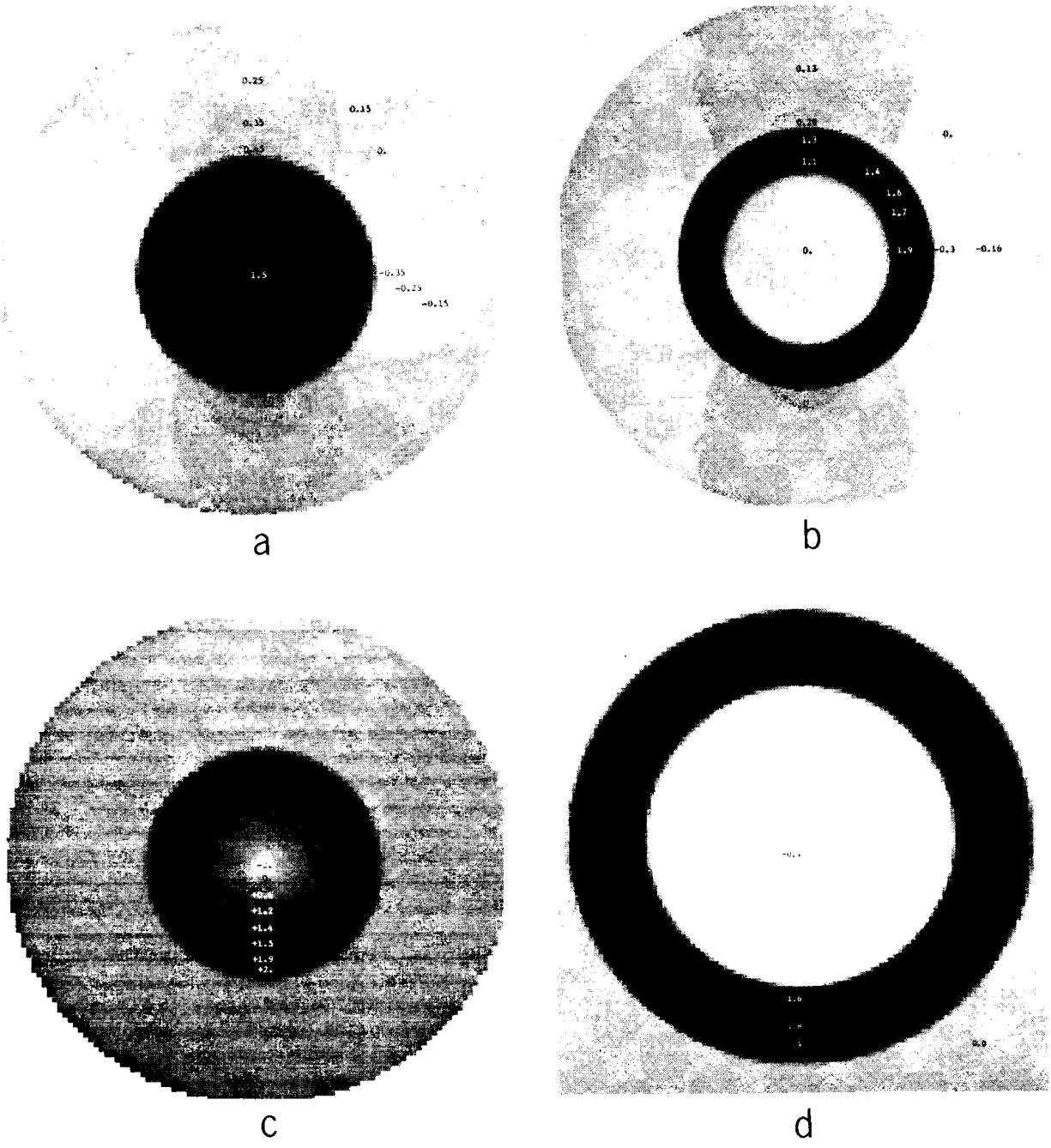


Figure 2. Effects of 2-to-1 anisotropy on tomographic reconstruction are illustrated for simple object geometries by simulation. Panels a) and b) are a disc and annulus with linearly-directed anisotropy; the correct values in the objects should be 1.0, and outside 0.0. Panels c) and d) are a disc and annulus with tangentially-directed anisotropy; again the values should be 1.0 within the objects and 0.0 outside but are severely corrupted by the anisotropy.

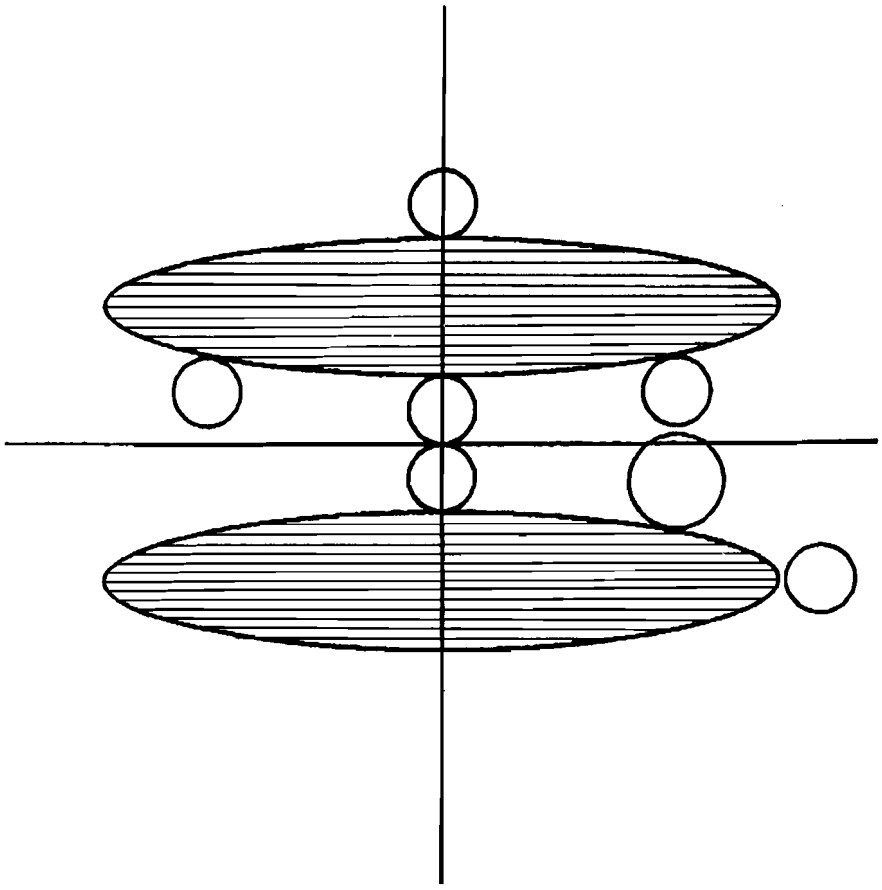


Figure 3. To demonstrate the effects of anisotropic objects in a tomographic reconstruction, the collection of circular and elliptic objects, shown schematically here, are reconstructed in Figures 4 and 5. The circular objects are intrinsically isotropic with a value of 0.5. The ellipses possess 2-to-1 anisotropy with linearly directed axes parallel to the lines shown.

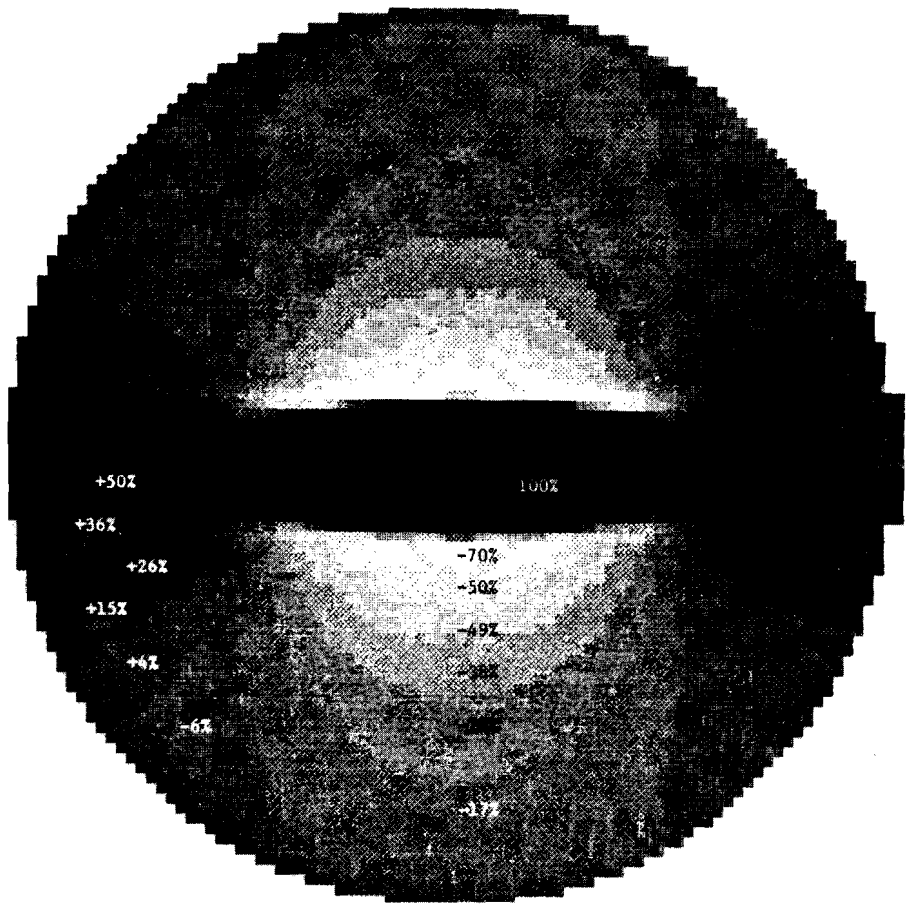


Figure 4. The effect of 2-to-1 linearly directed anisotropy in an isolated ellipse is demonstrated in this tomographic reconstruction. Reconstructed values outside the ellipse are expressed as a percentage of the value reconstructed in the ellipse (1.0); these values differ from the correct value of zero due to the anisotropy of the ellipse.

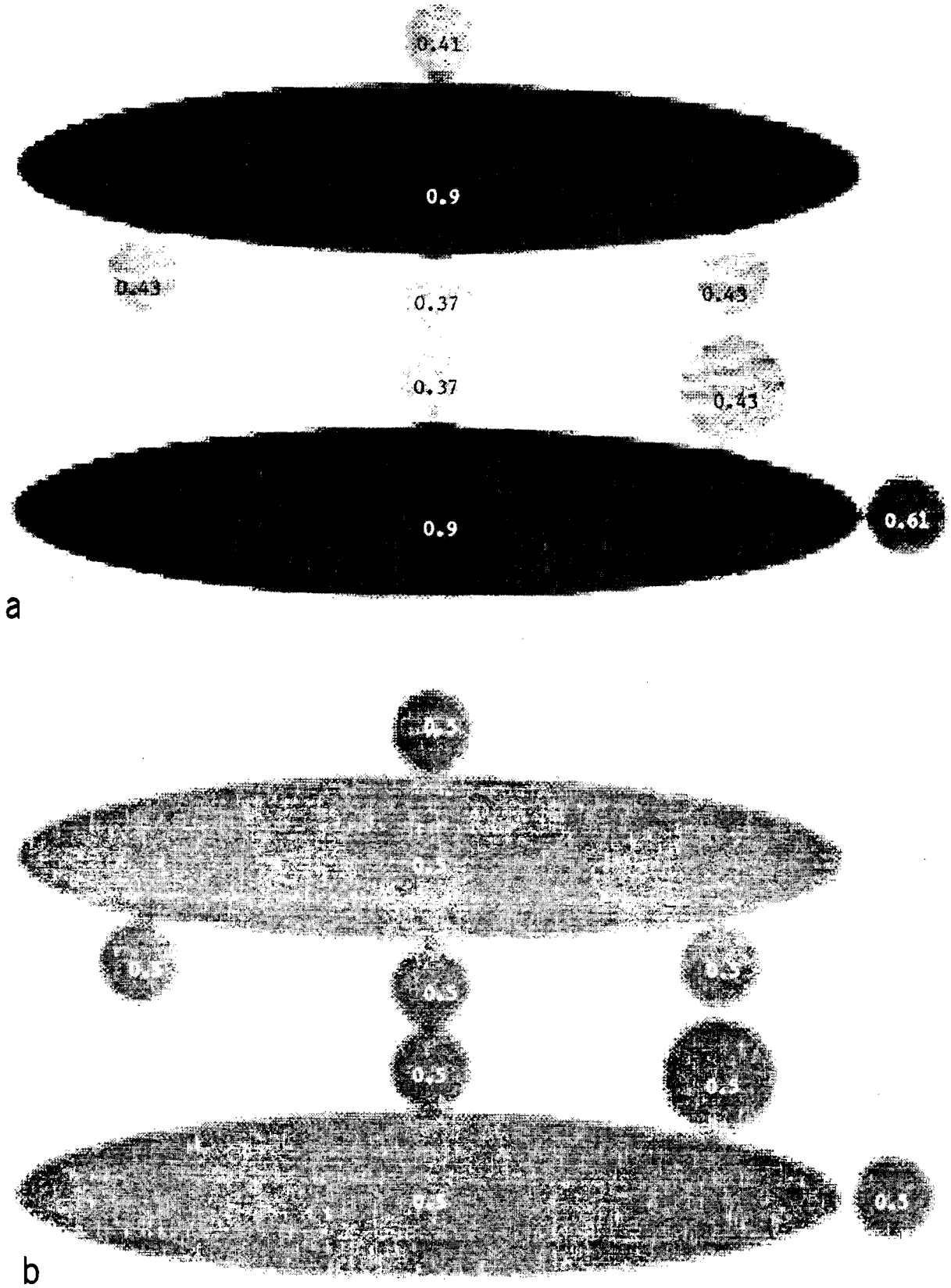


Figure 5. The collection of objects depicted in Figure 3 are reconstructed here. Circular objects are isotropic with value 0.5. In panel a) the anisotropy of the ellipses causes the isotropic discs to suffer both over and under estimation. Panel b) shows the same objects reconstructed from data in which all objects were intrinsically isotropic; the correct reconstructed values are shown.

of anisotropic objects on adjacent regions. Panel b) is a reconstruction of objects with the same geometry, but with strictly isotropic attenuations $\alpha_o = 0.5$ (β=0). The grey scale imaging window for panels a) and b) was selected with the $\alpha_o = 0.5$ at mid range so as to show both over and under estimations of the reconstructed attenuation.

III. Implications for Ultrasonic Tomography of the Heart

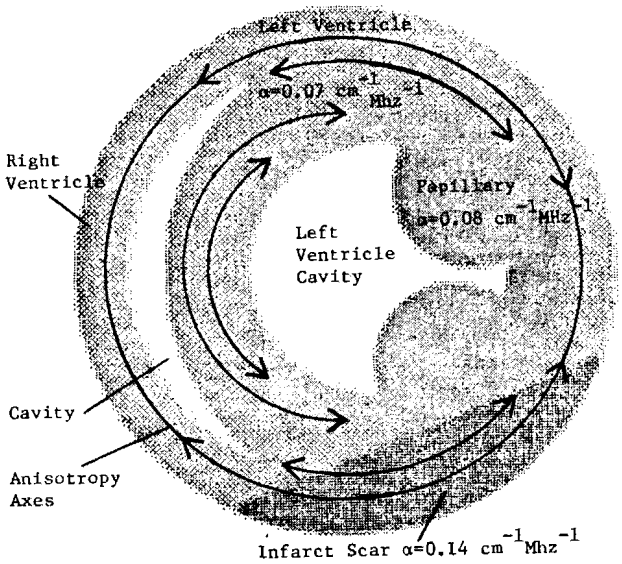
The recent tomographic study of dog hearts in vitro (B-2) demonstrated the capability of delineating regions of infarct in images based on attenuation and on time-of-flight measurements. Implications of anisotropy for attenuation images of the heart are studied by simulations based upon the 2.6-to-1 anisotropy observed in myocardium and the sinusoidal model.

Figure 6a is a schematic representation of a hypothetical slice through the ventricles of a dog heart. A photograph of an actual heart, in panel b), reveals the right and left ventricular cavities, papillary muscles in the left ventricle, and a white fibrous region in the posterior left ventricular muscle corresponding to scar tissue from an experimentally induced infarct. The plane of the image is oriented approximately perpendicular to the septum, as are many of the published tomograms.

Within the layers of the left ventricle, muscle fibers will be oriented in various directions, parallel to or oblique to the plane of the image. As a simplifying worst case, we model the fibers as parallel to the page. The papillary muscle fibers are modeled as perpendicular to the plane.

Projection measurements of the slice in this plane will view anisotropic myocardium in the ventricles and septum, but the interrogating wave propagates approximately normal to the papillary muscle fibers for all view angles, and therefore papillary muscle will appear isotropic.

In light of the geometry dependence of anisotropy effects, we illustrate the potential effects of anisotropy in tomographic reconstruction of the heart with a simulated model of an entire heart slice, corresponding to the schematic heart in Figure 6a. Illustrated, for comparison, in Figure 7 panel a) is a reconstruction of the slope of attenuation for the heart model without intrinsic anisotropy (β=0). Slope values correspond to independent measurements made in transmission, perpendicular to the muscle fibers. The effect of a 2:1 circumferential anisotropy is illustrated in panels b) and c). Because the anisotropy of infarct scar has not been well characterized, we simulate infarct scar with 2:1 circumferential anisotropy (β=1) in panel b) and simulate isotropic (β=0) scar in panel c). The isotropic components of the slope of attenuation (α_o) in all regions are equal to the normal-incidence slope values employed in the isotropic heart in panel a). The tangentially directed anisotropy model was employed with 2:1 anisotropy (β=1) oriented along the circular axes shown in Figure 6a. We provide, for comparison, a reconstructed image of actual



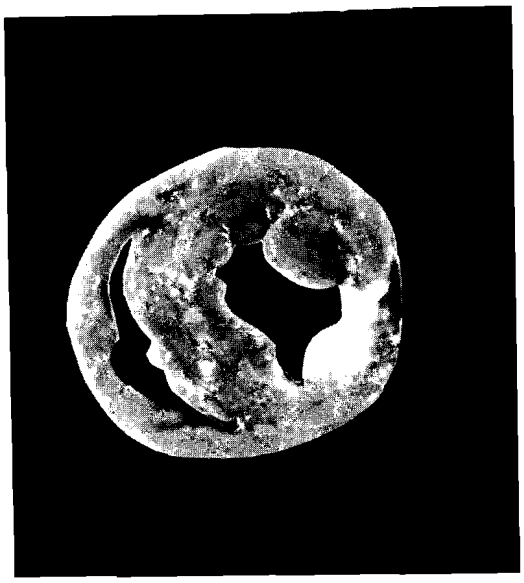


Figure 6. This schematic representation of a hypothetical slice through a dog heart in panel a) is to be compared with a photograph of an actual heart in panel b). The white fibrous region of the heart in panel b) corresponds to scar tissue from an artificially induced infarct. The values shown in panel a) represent values of the slope of attenuation from the literature. Anisotropy axes in panel a) represent the tangentially-directed anisotropy geometry values used in the simulations in Figure 7.

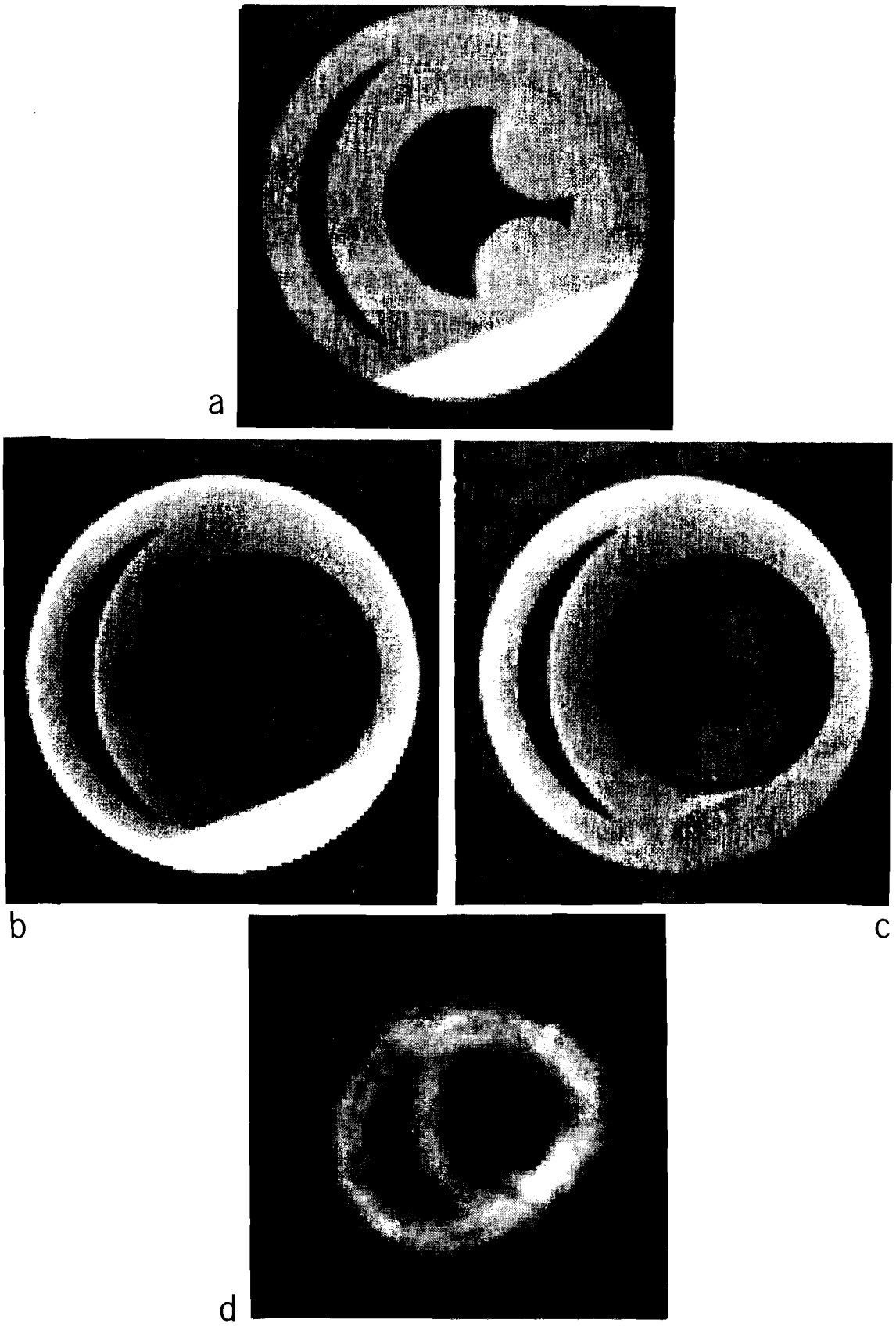


Figure 7. Simulated projections of a hypothetical dog heart are reconstructed to form images: Panel a) is an intrinsically isotropic model of a heart. Panel b) is a tangentially-directed anisotropic heart with infarct modeled as anisotropic. Panel c) is a tangentially-directed anisotropic heart with infarct modeled as isotropic. Panel d) is a reconstruction of the actual heart shown in Figure 6b.

tissue in d), based upon the slope of attenuation measured in the heart shown in Figure 6b.

We conclude:

1) Many of the errors encountered in tomographic reconstruction of the heart (such as underestimated values of attenuation in papillary muscle) derive from anisotropy.

2) Anisotropy constitutes a potential source of error in all ultrasonic imaging methods which employ multiple angles of view.

B-5. Adaptive Beamforming for Quantitative Ultrasonic Imaging

Personnel: R. M. Arthur, BCL
K. V. Gurumurthy, M.S., Electrical Engineering

Support: RR 00396
Washington University

Linear phased-array imaging systems have become commonplace in many clinical settings. Several advantages are gained by segmenting the transducer and controlling the delay or phasing of the elements in the array. Perhaps the most important advantages are that the beam can be steered over a larger area than the projection of the transducer and that it can be focused in the plane of the array. In order to steer and focus the beam delays are introduced between signals from the various elements before the signals are added to form a beam, which has been steered toward and focused on a region of interest. These delays are determined geometrically by assuming the medium is homogeneous. For qualitative imaging the homogeneous-medium assumption is satisfactory.

We tested the homogeneous-medium assumption for quantitative imaging and found that, even for simple geometries such as a two-layer model, it leads to large errors. In this case we assumed a 6-MHz source with a half-sine envelope had been produced by reflection at point P. Point P was 10 cm in front of the array and 5 cm to the side of its axis into the medium of interest. The layers were each 5 cm thick. That next to the transducer had an attenuation coefficient of 0.02 Nep/cm/MHz and a phase velocity of 1057 m/s. Corresponding values for the outer layer were 0.1 and 1536, respectively. The linear receiver was simplified to three points separated by 1 cm. We compared the results of combining signals from the receiver elements using the homogeneous-medium delays and of combining signals after properly aligning (or delaying) the signals with an adaptive beamformer. The peak amplitude of the two beamformer outputs varied by more than 6 dB.

Since the ultrasonic source was known, we could calculate its spectrum as shown in Figure 1a. To estimate the attenuation of that region as a function of frequency, we also calculated the spectrum after the ultrasound has passed through a tissue region. The result of this test is given in Figure 1b for the two-layer model described earlier. The adaptive beamformer estimates the attenuation coefficient to be 0.059 Nepers/cm/MHz. The average value along the three rays from source to receiver elements is 0.060 Nepers/cm/MHz. The homogeneous-medium beamformer, however, gives an estimate of the attenuation coefficient of 0.092 Nepers/cm/MHz, which is 3.7 dB too high. Thus even for very simple geometries the homogeneous-medium assumption appears to be inadequate for quantitative imaging. On the other hand, adaptive beamforming, at least in this example, permits an accurate assessment of attenuation as a function of frequency.

In our approach to adaptive beamforming the actual delays encountered by the ultrasonic field reflected from a particular point in the medium are estimated in order to correct the delays predicted by the homogeneous-medium assumption. The estimator can be implemented in several ways. Choice of the appropriate algorithm and technology for the estimator is a key goal of our on-going work.

The estimator we have tested and used to obtain the results in Figure 1 was a transversal filter with a length equal to the duration of the ultrasonic pulse. The received signal was shifted through the filter at uniform (10 ns) intervals. The filter was designed so that at each interval the filter output gave the amplitude of the characteristic frequency (6 MHz in this case) of the signal within the filter. A peak in this output corresponds to exact alignment of the pulse within the filter and thus estimates the actual delay of the pulse from the reflector to a given array element. Repeating this operation for each array-element signal permits the proper delays to be applied in each case. Thus phase cancellation across the array of the field from a particular reflector can be significantly reduced.

The primary assumption which governs the validity of this approach is that the field arriving at the receiver comes from a single point. To insure that only a small region generates a reflection, the insonifying beam must be tailored to focus the transmitted beam only on the region of interest. Development of the two-dimensional transducer as part of this work will permit such beam tailoring.

The two-layer simulation of inhomogeneous tissue used to illustrate the value of adaptive beamforming was based on a dispersive tissue model which links attenuation and phase velocity. While the effects of dispersion are small (1-2%) and can be neglected in the frequency domain, the inclusion of dispersion is essential for time-domain descriptions of tissue. The usual assumption of linear phase (constant phase velocity) leads to a non-causal impulse response. We developed a causal impulse response function using the Hilbert transform. The frequency response of a tissue sample of length ℓ and attenuation coefficient α_o at angular frequency ω is

$$H(\omega) = e^{\frac{-\alpha_o \ell}{2\pi}} e^{-j\theta(\omega)}. \qquad (1)$$

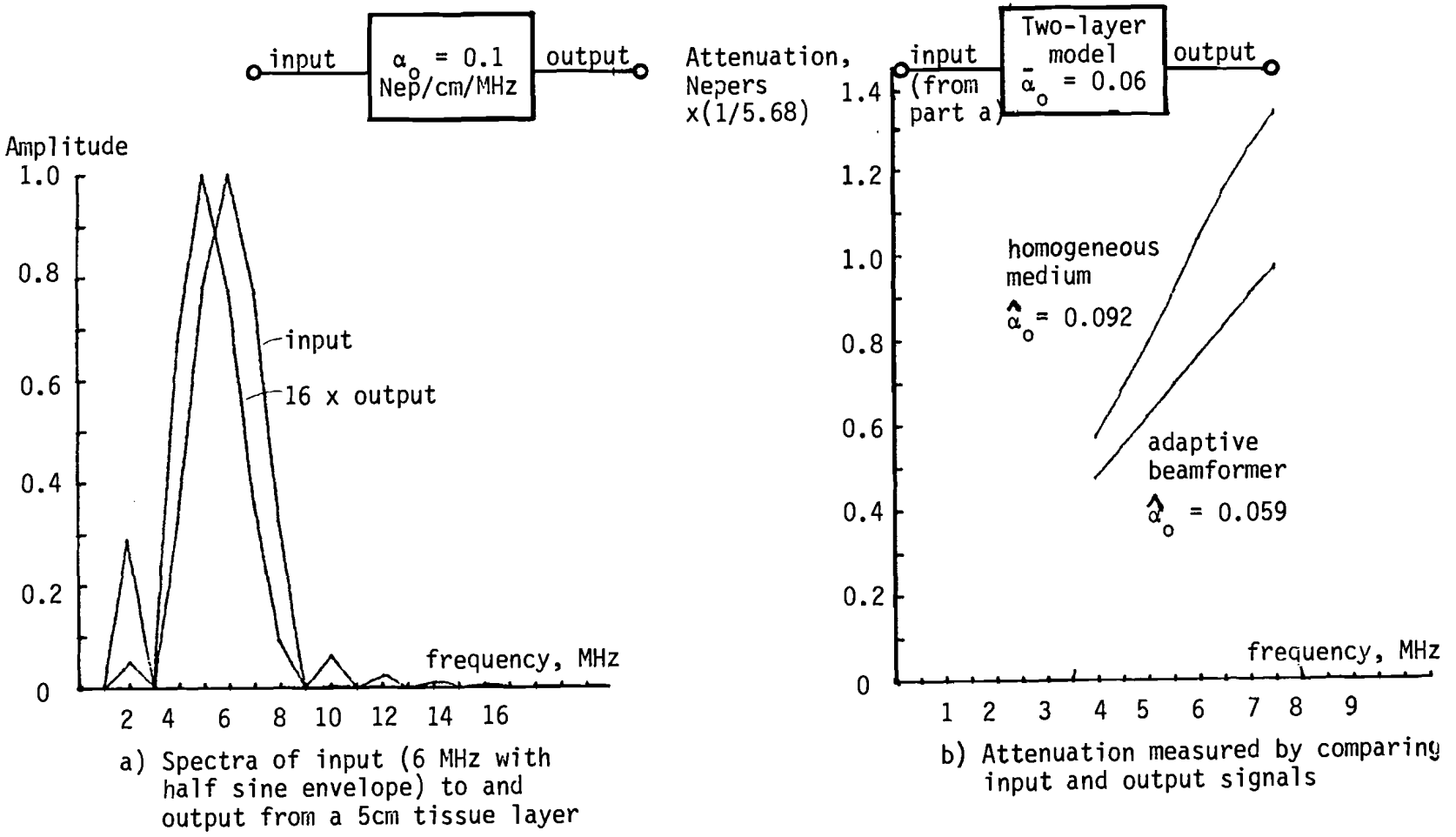


Figure 1. Effects on signals of a) Ultrasonic pulse propagation through tissue and b) Beamforming to estimate attenuation

The assumption of constant phase velocity makes $\theta(\omega)$ a linear function of frequency. If $|H(\omega)|$ satisfies the finite energy and Paley-Weiner conditions, then the Hilbert transform gives a minimum-phase expression for $\theta(\omega)$. The phase velocity becomes a function of frequency and α_o given by

$$Vp(\omega) = \frac{\omega}{\theta(\omega)} = \frac{\omega}{\omega\tau - \frac{\omega\alpha_o}{\pi^2}\ln(\omega)} \qquad (2)$$

where τ is the constant of proportionality in the linear phase expression, i.e., the bulk delay.

If the Hilbert phase term is substituted into the frequency response (Eq. 1), then a causal impulse response can be found by inverting $H(\omega)$. Estimates of α_o from the RMS duration of the non-causal impulse response are about 3 dB low. The attenuation coefficient is correctly predicted from the causal impulse response.

We have generalized the procedure for linking attenuation and phase velocity in a dispersive model, so that the frequency response is not restricted to the functional form of Eq. (1). By polynomial fitting any measured magnitude of $H(\omega)$, then extracting roots of the polynomial, we can find the poles and zeros of $H(\omega)$ under minimum-phase conditions. $H(\omega)$ can then be inverted to find the impulse response.

B-6. PETT IV Cardiac Studies

Personnel: B. E. Sobel, M.D., Medicine
E. M. Geltman, M.D., Medicine
J. A. Johnson, BCL
J. Markham, BCL
M. M. Ter-Pogossian, Ph.D., Radiology
T. J. Weadon, BCL
M. J. Welch, Ph.D., Radiology

Support: RR 00396
HL 13851
HL 17646

This project is designed to determine whether positron emission transaxial tomography (PETT) permits delineation of regional myocardial metabolism in vivo, with particular emphasis on zones of jeopardized ischemic myocardium and infarction. The overall objective is to provide a diagnostic modality quantitatively superior to conventional procedures based on assessment of cardiac biochemistry in vivo and to provide an investigative tool that will permit objective assessment of the efficacy of therapeutic interventions in diminishing the progress of ischemic injury to myocardial necrosis. Previously we have demonstrated that ^{11}C-palmitate is a particularly useful radionuclide for external assessment of myocardial metabolism. Fatty acid is the preferred substrate of the heart for a variety of reasons, including the high cytoplasmic ratio of carnitine to CoA which leads to conversion of activated fatty acids to species that can ingress into the mitochondria where oxidation takes place. We have previously demonstrated that the externally detectable reduction of ^{11}C-palmitate accumulation in perfused hearts correlates closely with hypoxia and its metabolic sequelae despite the maintenance of constant flow. In addition, we found that the distribution and extent of myocardial infarction detectable tomographically with ^{11}C-palmitate administered intraveneously into intact dogs correlates closely with myocardial infarction quantified morphometrically at necropsy and delineated with the use of enzyme assays applied to contiguous cross sections of the heart. A series of completed studies has defined the consistency of lipid pools in heart muscle, the relationships between altered retention of ^{11}C-palmitate and metabolic integrity reflected by generation of CO_2, and physiological determinants of myocardial oxygen requirements in relation to oxidative rates of ^{11}C-palmitate detected externally.

The feasibility of tomographic delineation of healed myocardial infarction was demonstrated first in studies with PETT III. Initially, we found that the distribution of ^{11}C-palmitate in cross sections of the heart from normal subjects was homogeneous but that zones of diminished uptake characteristically occurred in patients with healed myocardial infarction in locations corresponding to the electrocardiographic locus

of the infarct. More recently, studies performed with PETT IV demonstrated that delineation of the blood pool after inhalation of ^{11}CO enhanced recognition of the endocardial border and facilitated quantification of the extent of jeopardized, ischemic myocardium based on its diminished uptake of ^{11}C-palmitate. During the past year, a close correlation was observed between enzymatically and tomographically estimated infarct size among patients with either transmural or subendocardial infarctions. Among 11 patients with non-transmural infarction defined electrocardiographically who were studied one to eight weeks after the onset of symptoms, regional depressions of ^{11}C-palmitate accumulation (<50% of maximum mural uptake) were detected with sagittal, coronal, and transaxial reconstructions and quantified based on activity in 14 transaxial sections obtained from each patient. Since regional wall motion abnormalities detectable by conventional scintigraphy corresponded to zones of metabolic impairment, these results indicated that regional wall motion disorders depend on irreversible metabolic dysfunction to a considerable extent in patients with ischemic heart disease.

Studies in progress are designed to clarify the extent to which metabolic abnormalities of fatty acid metabolism characterize and perhaps contribute to the pathogenesis of entities other than ischemic disease such as cryptogenic cardiomyopathy, to determine whether regional myocardial perfusion can be assessed with the methods developed and undergoing evaluation in experimental animals in correlative studies with PETT V, and to localize regions of ischemia manifested by metabolic impairment with stress in order to noninvasively detect entities such as left main coronary disease.

B-7. Positron Tomographic Imaging of the Liver with PETT IV

Personnel: B. Kumar, M.D., Radiology
G. J. Ehrhardt, Ph.D., Radiology
J. Markham, BCL
C. J. Mathias, B.A., Radiology
T. R. Miller, M.D., Radiology
B. A. Siegel, M.D., Radiology
M. J. Welch, Ph.D., Radiology

Support: EV 04318
HL 13851
HL 17646

A new radiopharmaceutical, ^{68}Ga-iron hydroxide colloid, for hepatic imaging by positron emission tomography (PETT) was prepared from the eluate of a ^{68}Ge-^{68}Ga solvent-extraction generator. In rats, 84% of

the administered dose of colloid localized in the liver and 4.6% accumulated in the spleen. Initial imaging studies in normal dogs showed close correspondence of the findings by PETT and transmission computed tomography (CT). PETT with ^{68}Ga-colloid was performed in 10 patients with hepatic metastases demonstrated by conventional scintigraphy with ^{99m}Tc-sulfur colloid images were demonstrated by PETT. The positron tomographic images were compared with those obtained by CT in seven patients; the two studies showed comparable findings in five patients, whereas PETT more clearly showed multiple lesions in two. Our results suggest that PETT is a suitable technique for obtaining high-contrast, cross-sectional images of large abdominal organs.

B-8. PETT V Experimental Studies

Personnel: B. E. Sobel, M.D., Medicine
H. D. Ambos, BCL
S. R. Bergmann, Ph.D., Medicine
J. O. Eichling, Ph.D., Radiology
R. A. Lerch, M.D., Medicine
J. Markham, BCL
M. M. Ter-Pogossian, Ph.D., Radiology
M. J. Welch, Ph.D., Radiology

Support: RR 00396
HL 13851
HL 17646
NS 06833

The overall goal of this project is to implement and evaluate procedures required to translate to intact animals the results obtained with selected positron-emitting tracers used to characterize metabolism and perfusion in isolated hearts in which the distribution of tracer and the time course of its clearance from myocardium can be quantified by fast-scan positron-emission tomography. Such studies are intimately related to the clinical activities being undertaken with PETT IV in which static imaging is possible. On the other hand, it has become clear to us that a great deal of additional information can be obtained with sequential positron emission tomography utilized to characterize the time course of uptake, accumulation, and clearance of tracers whose physiological behavior has been characterized in well controlled preparations.

Since regional metabolism of exogenous fatty acid extracted by myocardium has been shown to depend primarily on oxidation, a recent study was performed to determine whether viable but ischemic tissue could be detected and localized in vivo based on external detection

of its impaired fatty acid metabolism. Regional clearance of ^{11}C-palmitate was assessed by sequential tomography in 15 anesthetized dogs. Clearance was consistently exponential from 5 to 15 minutes after administration of tracer intravenously. In the absence of coronary stenosis, clearance was homogeneous throughout the heart with an average coefficient of variation (CV) of only 11 $\pm$ 2%. Homogeneity persisted when heart rate was increased by pharmacological agents from 84 $\pm$ 6 to 222 $\pm$ 11 beats/min. With subcritical left circumflex coronary stenosis (reduction in vessel diameter of 70% or less) homogeneity of ^{11}C-palmitate clearance under control conditions and with tachycardia did not differ from that seen in hearts without coronary stenosis. However, with critical stenosis (reduction in vessel diameter exceeding 70%) sufficient to induce ischemia without gross infarction, regional ^{11}C-clearance became markedly heterogeneous under control conditions and even more strikingly so with induced tachycardia. The heterogeneity resulted from a reduction of ^{11}C-clearance in regions supplied by the stenotic vessel compared to clearance in well perfused zones. Thus, sequential positron emission tomography after intravenous injection of ^{11}C-palmitate delineated zones of viable, ischemic myocardium that characteristically exhibited impaired oxidation of extracted fatty acid.

Studies are in progress to analyze errors likely to be encountered with this approach in patients with coronary artery disease. Computer simulation is being employed to define errors related to limitations of resolution, movement artifact, changes in wall thickness, and diffusibility.

The studies with ^{11}C-palmitate address the question of whether or not altered metabolism is a consistent consequence of ischemia (under conditions of rest or with stress) and to determine whether or not such alterations can be used to localize jeopardized tissue in a reproducible fashion. Additional work is evaluating the need to quantify regional perfusion with a noninvasive technique devoid of the difficulties encountered with single photon scintigraphy. Such difficulties include superposition of myocardium in several dimensions on a two-dimensional display, the non-physiological nature of tracers employed, variation in tracer extraction fraction as a function of flow due to altered residence time, and variable attenuation as a function of depth in non-homogeneous biological systems. The tomographic studies in progress with PETT V are predicated upon results obtained in studies of isolated perfused hearts. With the use of a tracer selected to partition evenly between blood and tissue (^{11}C-butanol) and programmed exponential infusion to achieve a steady-state value of a function derived from the monotonically increasing tissue concentration of tracer measured over time, we were able to demonstrate in isolated perfused hearts that myocardial perfusion could be assessed accurately and quantitatively by external detection of accumulated radioactivity. Application of this approach to intact experimental animals and ultimately to patients will require the use of very rapid scanning instrumentation with sensitivity sufficient to avoid large radiation burdens and provide adequate resolution despite the need for gating. Presently a quantitative

analysis is in progress employing computer simulation of potential errors that might be encountered in such an approach including those attributable to diffusibility of tracer, limitations of resolution of the instrument, movement artifact, and contributions of tracer within the blood pool to activities within the field of view (partial volume effects). In addition, experiments are being undertaken to compare regional estimates of perfusion based on sampling myocardium and assay of the distribution of radiolabeled microspheres to estimates of perfusion derived from positron-emission tomography coupled with programmed, exponential infusion of tracers administered intravenously.

In order to assure that interpretations of the results of tomography are consistent with actual events within the tissue, correlative studies are being undertaken with the use of a probe applied to the surface of the heart that is capable of detecting the emitted positrons per se rather than the gamma radiation due to annihilation. With the use of the probe, and with an experimental design that permits imposition of selected rates of perfusion in specific regions of myocardium with verification employing electromagnetic flowmeter determinations and/or assessment of the deposition of radiolabeled microspheres, determinations of error bounds likely to apply to interpretation of results of tomographic studies in vivo are being obtained.

B-9. PETT VI Development

Personnel: D. C. Ficke, B.S., Radiology
G. E. Bickmore, Radiology
C. S. Higgins, A.B., Radiology
J. T. Hood, B.S., Radiology
J. Markham, BCL
N. A. Mullani, BCL
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851
NS 06833

The newest generation of positron emission tomographs is represented by PETT VI. As was the case for its predecessor, PETT V (PR 14, B-5; PR 15, B-5), the development of PETT VI is targeted at producing fast dynamic scans which exhibit high spatial resolution and sensitivity in human cerebral and small animal studies.

PETT VI features cesium fluoride (CsF) scintillation detectors.[1] Count rate limitations imposed by the deleterious effects of random coincidences have been greatly reduced if not practically eliminated by this fast timing crystal.

Due to relatively low light output from the CsF and the desire to maintain fast timing, individual detectors and associated electronics have been chosen in favor of the positioning circuit implementation of both PETT IV and PETT V. In order to achieve an economy of space and interconnecting hardware, a gantry-mounted electronics channel has been developed whereby each CsF detector has its own photomultiplier tube, wideband amplifier, constant fraction discriminator, and timing delay.

Table 1 contains specifications for PETT VI. The construction of the machine is essentially complete. Final debugging, calibration, and programming will continue through the third quarter and formal studies are planned for the fourth quarter of 1980.

1. N. A. Mullani, D. C. Ficke, and M. M. Ter-Pogossian, "Cesium Fluoride: A New Detector for Positron Emission Tomography," IEEE Transactions on Nuclear Science, vol. NS-27, no. 2, pp. 572-575, 1980.

Table 1

PETT VI SPECIFICATIONS

Geometry	Circular array consisting of 4 rings of 72 detectors yielding 7 simultaneous slices
Detectors	CsF (2.0 x 2.4 x 6.5) cm
Motion	Wobble and rotate
Scan Time	Integrals of 1 sec
Resolution	12 or 7 mm
Slice Thickness	14 mm
Aperture size	30 cm
Field of View	27 cm
Sensitivity	7 slices of 12 x 14 mm resolution yield 325,000 counts/sec/μCi/cc in 20 cm diameter phantom
Detector Time Resolution	1.5 nsec FWHM
System Time Aperture	6 nsec

B-10. PETT Time-of-Flight Data Acquisition System

Personnel: N. A. Mullani, BCL
G. J. Blaine, BCL
D. C. Ficke, B.S., Radiology
J. Markham, BCL
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
Washington University

Positron-emission transaxial tomographic scanners produce cross-sectional images of the body showing the spatial distribution of positron-emitting radionuclides which are concentrated by biochemical or physical processes in regions of interest. Utilization of PETT for dynamic imaging within the thorax and the head have necessitated technological developments which improve instrument sensitivity as well as decrease radiation dosages to patients and provide shorter scanning durations.

The current development of a new instrument, Super PETT, utilizing scintillators of cesium flouride[1] (CsF) and a high-speed acquisition and preprocessing system will utilize information about the differential time of flight of annihilation photons to achieve a sensitivity improvement of a factor of ten or better over the current thoracic scanner PETT IV. Experiments and theoretical studies of reconstructions based upon time-of-flight data have been initiated (B-11, B-12, B-13).

A new approach to data acquisition is required to achieve high precision (sub-nanosecond) coincidence-timing resolution and to cope with high data rates to be generated by a proposed instrument configuration in which detectors are to be grouped in four rings of 96 units each. Initial design studies have been conducted to establish the feasibility of including preprocessing tasks for both projection and time-of-flight data within the acquisition system. Partitioning the acquisition system on a processor-per-slice basis reduces the anticipated data rate to less than 200,000 events-per-second per processor. A specialized processor architecture, based on bipolar bit-slice technology, will provide on-line detector-pair sensitivity normalization, wobble-position correction, position-coordinate transformation, time-of-flight correction, and accumulation of both and time-of-flight arrays. The collected arrays will then be transferred to a supporting computer system for data reconstruction and display.

1. N. A. Mullani, D. C. Ficke, and M. M. Ter-Pogossian, "Cessium Flouride: A New Detector for Positron Emission Tomography," Journal of Nuclear Medicine, in press.

B-11. Tomography Reconstruction Algorithms for PETT Time-of-Flight Data

Personnel: D. L. Snyder, BCL
N. C. Cheng, BCL
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851

At least two approaches can be identified for deriving reconstruction algorithms for differential time-of-flight data in positron emission tomography. The first uses a deterministic model for the data, which is equivalent to assuming an infinite "signal-to-noise ratio" or an infinite number of coincidence detections. This approach has been used by investigators in France at the Laboratorire d'Electronique et de Technologie de l'Informatique to give an intuitive argument for an algorithm in which the image is generated by two-dimensional filtering. During data acquisition, an unfiltered time-of-flight "pre-image" is created by adding each coincidence event into a preimage array at the location indicated by the line connecting the two scintillation detectors involved with the position along this line indicated by the differential time of flight measured. This procedure produces a blurred pre-image which has a resolution between that along the coincidence line due to the uncertainty in the time of flight and that perpendicular to the coincidence line due to the line-spread function for the detectors and collimation being used. This blurred pre-image can then be filtered two dimensionally to reduce the blurring and produce the final reconstructed image. A two-dimensional filter can be specified intuitively using a deterministic model; it consists in the spatial frequency domain of a $|\rho|$ filter, to compensate for the projection process, cascaded with a filter to compensate for the time of flight uncertainty. This approach is presently being investigated with experimental data, and the results are quite encouraging (see B-13). There are at least two potential disadvantages with this approach. One is that a deterministic model for time-of-flight data does not appear to lead to a mathematically unique algorithm as it does with conventional tomography. The second difficulty is that two-dimensional filtering has not proven to be sufficiently efficient to be useful in tomographic reconstructions from projection data, so it may not be for time-of-flight data either. Another approach is simply to derive projection data from time-of-flight data and then use any existing tomography algorithm, which in effect ignores the additional useful information in time-of-flight data but without any performance loss in the infinite signal-to-noise ratio limit.

A second approach for developing algorithms for time-of-flight data is to use nondeterministic models. This approach has the advantage of allowing the large uncertainty in time-of-flight data, the fluctuation statistics in annihilation event times, and the finite but random number of coincidence events to be taken into account. We have initiated an effort to develop an algorithm by postulating a probabilistic model and using the maximum-likelihood method of statistics to estimate image

parameters. Our preliminary results are briefly summarized as follows. The data for a single coincidence event is $(D_{i,j},u)$, where $D_{i,j}$ identifies the detector pair and u is the measured position of the event along the line that connects detectors i and j. This measured position is in error by an amount ε along the connecting line; we let $g(\varepsilon)$ denote the probability density of this error. We assume that the image to be reconstructed consists of the piecewise constant M×M array; the unknown parameter λ_i in the ith pixel is the concentration of tracer in that resolution cell. Additionally, we assume that coincidence detections are mutually independent events, that coincidence detections occur as a Poisson point process, and that there are no random detections due to photon pairs not originating from annihilations. The last assumption is the most severe but can probably be removed as the study proceeds. The algorithm results by solving the following problem. Given $g(\varepsilon)$, the above assumptions, and the time-of-flight data

$$(D_{i_n,j_n},u_n: n=1, 2, \ldots, n_t),$$

where n_t is the total number of detection events, find the parameters

$$\underline{\lambda} = (\lambda_1, \lambda_2, \ldots, \lambda_{M^2})$$

that maximize the probability of acquiring this data. Our preliminary findings in solving this problem are as follows. Without loss in performance, the data can be processed as they are acquired to form the same pre-image as used in the deterministic algorithm described above; thus, in the ith resolution cell, there will be a total of n_i detection events measured. If $\underline{\lambda}$ denotes the maximum likelihood estimate of the M^2 image parameters, then we find that $\hat{\underline{\lambda}} = \underline{A}^{-1}\underline{n}/n_t$, where

$$\underline{n} = (n_1, n_2, \ldots, n_{M^2}),$$

and $\underline{A}$ is an $M^2 \times M^2$ precomputable matrix with k,m element given by

$$a(k,m) = \Delta^2 \frac{N(k,m)}{N(m,m)} \iint g(\varepsilon) I_k(U_m + \varepsilon v_{k,m}) d\varepsilon,$$

where Δ is the dimension of a resolution cell, N(k,m) is the number of lines connecting detector pair that pass through cells k and m, N(m,m) is the number of these lines passing through cell m, $I_k(u) = 1$ if u is in cell k and $I_k(u) = 0$ otherwise, U_m is the center position in cell m, and $v_{k,m}$ is a unit vector from cell k to cell m. It is important that the inverse of $\underline{A}$ is precomputable because this matrix is of large dimension, and the computation of $\underline{A}^{-1}$ will require care and considerable computation. We are presently investigating the properties of the matrix $\underline{A}$. It appears that $\underline{A}$ can be blocked into Toplitz submatrices and that efficient algorithms

for its inversion exist. Further study is needed to discover what benefit these observations may have in rapidly creating tomography images from time-of-flight data.

B-12. Signal-to-Noise in Positron Emission Time-of-Flight Tomography

Personnel: D. L. Snyder, BCL
N. C. Cheng, BCL
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851

We have initiated an effort to predict the signal-to-noise ratio performance of the maximum likelihood algorithm described in (B-11). Our preliminary results in predicting the performance of this algorithm indicate that if σ_i^2 is the mean square error in estimating the ith pixel value λ_i, then the noise-to-signal ratio is given by

$$\sigma_i^2/\lambda_i^2 = E(1/n_t)[\sum_{m=1}^{M^2} b^2(i,m) \sum_{j=1}^{M^2} a(m,j)\lambda_j\lambda_i^{-2} - 1],$$

where b(i,m) is the i,m element of $\underline{A}^{-1}$. At the present time we are attempting to evaluate this expression as a function of the time-of-flight uncertainty and to compare the result with the corresponding performance for a conventional tomography reconstruction of the same image.

B-13. PETT Time-of-Flight Experimental Studies

Personnel: J. Markham, BCL
N. A. Mullani, BCL
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851
HL 17646

A feasibility study was conducted to demonstrate the improvement in image quality with the use of time-of-flight (TOF) information in positron emission tomography (PETT). In conventional tomography, events along a coincidence line can occur anywhere along that line; in TOF tomography, the location of the origin of the annihilation can be estimated from the

difference in the times of arrival of the two photons at opposing detectors. Due to present technological limitations, the uncertainty in the measured time difference is 500-1000 picoseconds or an uncertainity in position of several centimeters.

Two experiments were conducted using two fast cesium-fluoride detectors with a time resolution of 600-800 picoseconds FWHM (full width half maximum) equivalent to an uncertainity in position of 9-12 cm. For the first study a point source was scanned every 0.5 cm for 2 cm yielding 5 parallel projection or coincidence lines. Each projection line was divided into intervals of 0.67 cm, and the time-of-flight information was used to place each coincidence event in the appropriate interval. The time-of-flight resolution along each projection line was 9 cm FWHM and the physical resolution in the direction perpendicular to the projection lines was 1.6 cm FWHM. A time-of-flight image was generated from these 5 projection lines by using the same set of data for different projection angles, i.e., by rotating the data about the center of the point source. The resolution of the resulting unfiltered TOF image was 2.2 cm FWHM, 0.6 cm more than the physical resolution of 1.6 cm FWHM.

The second experiment utilized a 42-cm phantom consisting of three concentric rings with relative activity levels of 1, 0, 5. The TOF resolution for this study was 12 cm FWHM. A single scan of 22 parallel projections, 1 cm apart, was performed with each projection line divided into intervals of 0.83 cm for the TOF data. Because of the symmetrical nature of the phantom, the same scan data were used at 90 different angles to reconstruct an TOF image with a 50 cm field of view (100 × 100 elements). After reconstruction, a two-dimensional filter was applied to the TOF image. The same scan data were used to reconstruct an image in conventional mode using filtered back-projection. The cutoff frequency for the two filters was the same. Figure 1 shows the two reconstructed and filtered images. The TOF image shows significant improvement in the reduction of background activity in areas of no activity.

We have shown that an improvement in image quality can result from using TOF information, even with the present uncertainty of several cm in the measured position of the annihilation. This improvement will be especially important for whole-body scanning where the amount of scattering and attenuation contribute to considerable smearing of areas of higher activity.

a. b.

Figure 1. Reconstructed images of a 42 cm phantom consisting of three concentric rings with relative activity levels of 1, 0, and 5.

a. Conventional reconstruction using filtered back-projection.
b. TOF reconstruction with two-dimensional filtering.

B-14. Algorithm Development for Radiation-Treatment Planning

Personnel: K. B. Larson, BCL
R. J. Arnzen, BCL and Computer Systems Laboratory
W. C. Chen, BCL
R. E. Hitchens, BCL
C. A. Pérez, M.D., Radiology
S. C. Prasad, Ph.D., Radiology
J. A. Purdy, Ph.D., Radiology
F. U. Rosenberger, D.Sc., Computer Systems Laboratory
L. J. Thomas, Jr., BCL

Support: RR 00396
Washington University

We have previously established the physical validity of our "data-volume" method of computing three-dimensional absorbed-dose distributions in inhomogeneous media using differential scatter-air ratios (PR 13, I-3; PR 14, G-6; PR 15, G-4). Accordingly, we have shifted our attention to the objective of applying advanced digital systems to render our method practical in a clinical setting. As a result, our algorithmic work during the past year has consisted of identifying and making appropriate modifications that 1), allow computations to be made with electron-density matrices of clinically realistic sizes and shapes, including those obtained by computed-tomography scans of the RANDO phantom (PR 14, G-6) and 2), decrease the total time required to compute an individual three-dimensional dose distribution by measures such as replacing all function evaluations by equivalent table look-up procedures, eliminating redundant computations, and incorporating efficient means for computing coordinates of volume elements in the electron-density matrix. With the expectation of using macromodules[1] to realize a practical implementation for these algorithms, we have rewritten all our programs in fixed-point arithmetic, and have demonstrated resulting computational accuracies comparable with those achieved previously using floating-point arithmetic.

Our most efficient algorithms for computing absorbed-dose distributions require the use of three-dimensional rectangular coordinates to form memory addresses for the electron-density and differential scatter-air-ratio (SAR) matrices. Because the available SAR data are presented in the right circular-cylindical coordinate system, we are currently transforming these data to the Cartesian system so that we can use them in our algorithms.

1. C. E. Molnar, F. U. Rosenberger, and R. A. Arnzen, "Macromodular Computer Design. Part 3: Restructured Macromodules," Final Report, Contract SD-302 (ARPA), Computer Systems Laboratory, Washington University, St. Louis, Missouri, February 1974.

B-15. Macromodular System and Array Processor Implementations for Absorbed-Dose Calculations in Radiation-Treatment Planning

Personnel: R. J. Arnzen, BCL and Computer Systems Laboratory
W. C. Chen, BCL
V. W. Gerth, Jr., BCL
R. E. Hitchens, BCL
K. B. Larson, BCL

Support: RR 00396

Development of a restructured macromodule system for implementation of the "delta-volume" algorithm (PR 13, I-3; PR 14, G-6; PR 15, G-4) will permit three-dimensional dose computations to be carried out in a timely manner for the radiation therapist engaged in developing a treatment plan. The macromodular system currently under development for this purpose will be working in conjunction with a Texas Instruments 980 computer. This system has been designed to exploit the concurrency potential in the "delta-volume" algorithm.

Currently, the primary role of the macromodules in the system is to compute the exponent of the attenuation function for all primary and scattered rays. Simultaneously, the TI-980 will process the previous macromodular computation. Splitting the processing task at this point allows us to achieve similar execution times for the two processors of approximately 40 μs. It will therefore require us about six minutes to complete an entire dose distribution for a 16^3-cm^3 volume.

The macromodules used in this system are drawn from the current inventory of types. The kernel of the macromodular system consists of three sections, each of which is allocated a specific processing task, with all operating in parallel. One section, which incorporates a macromodular memory containing electron-density information from computed-tomography scans, computes the line integral of the electron density for the exponent of the attenuation factors. For this purpose, it utilizes a newly developed algorithm for voxel identification. This process, which is the slowest of the three, requires approximately 15 μs to complete a voxel-pair computation. The second process is a simple table look-up to determine the size of the differential element of ray-path length for the line integral. A single macromodular memory is used for this look-up. The address is formed by the concatenation of the x, y, and z increments for the particular voxel pair. This process takes about 1 μs to complete. The third process determines the Klein-Nishina electron cross-section for the scattered ray. This process requires determination of the cosine of the angle between primary and scattered rays. For this determination, a coordinate-transformer module designed for use with the MMS-X Modeling System is ideally suited. The coordinate transformer is provided the x-, y-, and z-components of the primary and scattered rays. It then performs a vector dot-product operation and a scaling to produce the cosine of the angle between these rays. This quantity is then used as an address to a macromodular memory whose contents are the Klein-Nishina cross-sections. Approximately 10 μs are necessary for this operation.

Following the calculation of the line integral, differential element size, and electron cross-section, a second coordinate transformer is used to form the product of these three quantities. This product is then delivered to the TI-980 computer for updating the absorbed dose for the dose voxel.

Currently, the integration of the various pieces of the macromodular subsystems is under way. In addition, facilities for initial loading of macromodular memories and system initialization are being planned.

Along with our macromodular implementation efforts, we have also carried out a preliminary investigation of another implementation based on using our array processor working with its host computer. The array-processor memory would contain all data arrays and would do all calculations in floating-point arithmetic, except for pixel identification, which would use a fixed-point algorithm (B-14). As in the case of the macromodule system, the array processor would operate concurrently with the host computer. At this time, we have made no accurate estimate of total run time, but expect that we can achieve performances comparable with those of the macromodule system.

B-16. Three-Dimensional Display of Absorbed-Dose Computation for Radiation-Treatment Planning

Personnel: R. J. Arnzen, BCL and Computer Systems Laboratory
V. W. Gerth, Jr., BCL

Support: RR 00396

The MMS-X Modeling System has proven itself to be an effective tool for the crystallographer for visualizing complicated three-dimensional structures. An extension of the uses of the MMS-X for presentation of three-dimensional functions was carried out in an effort to determine whether or not this system will be suitable for visualization of computed dose distributions throughout an irradiated volume of tissue.

The method investigated employed a defocused CRT beam to give a diffused spot on the screen. The intensity of the spot is directly proportional to the computed dose at that point in space. The composite dose distribution then consists of "hot" and "cold" areas representing areas of high and low dose, respectively. The MMS-X graphics capabilities allow the resulting image to be rotated in space, thus providing the clinician with a view from any angle. In addition, a "zoom" or magnification function allows close-up views of areas of particular interest.

Results of initial experiments indicate that the use of a defocused beam for three-dimensional function representation is an effective technique for visualization. However, it is also desirable, if not essential, to include anatomical references along with the computed dose distribution. This

requirement demands a sharply defined beam. A possible solution to these conflicting goals is dynamic focusing under computer control. A study of this problem has been undertaken and it appears at this time that such a feature can be readily implemented. As yet no hardware has been constructed to this end.

B-17. Ventricular Boundary Extraction

Personnel: C. N. Carlson, BCL
G. J. Blaine, BCL
G. H. Brandenburger, BCL
J. G. Dunham, BCL
P. A. Ludbrook, M.D., Medicine
D. L. Snyder, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396

The analysis of angiographic images is used to establish the pathophysiologic implications of altered pressure-volume relations in ischemic myocardium. From the angiographic information, indices of both "global" function (ventricular volume, stroke volume, ejection fraction) and "localized" function (regional myocardial dynamics) of the ventricle may be obtained. Semi-automated analysis systems, which use operator "sketched" ventricular borders, have moved from research environments into a commercial computer-based catheterization laboratory system. A variety of algorithmic approaches specifically directed to the identification of the ventricular border have been reported in the literature, and the viability of computer-assisted determinations of left-ventricular borders has been demonstrated in the clinical environment at Latter Day Saints (LDS) Hospital. The LDS algorithm[1] and the Modestino algorithm[2] have been identified as promising candidates for study, implementation, and extension.

Both algorithms have been analyzed in some detail and timing estimates have been calculated. The estimates are summarized in Table 1. The tree-search estimate was based on a best-case performance and would be expected to increase with increasing image noise. Reported computation times for the LDS algorithm range from early results of 55 seconds per image to later results of 10 seconds per image for a CDC 3300 computer. Opportunities for concurrent computation were identified in both algorithms.

Availability of a moderately priced, high-performance raster-scan graphic processor, the Lexidata Model 3400, has enabled us to move the algorithm evaluation work to a PDP-11 based system for continued development. A software environment is evolving using RATFOR, the "RATional FORtran" preprocessor, FORTRAN, and MACRO-11 the PDP-11 assembly language. Image, image sequence, contour, and contour sequence file structures have been designed, implemented, and documented.

Table 1

Timing Estimates

	PDP-11/34 with floating point hardware	CSPI array processor
"LDS" algorithm	30 seconds	1.2 seconds
"Modestino" algorithm	25 seconds	--

An initial experiment using the Vanguard X-34 35 mm film projector and a GE charge-injection-device (CID) camera was utilized to digitize representative ventricular contours to qualitatively assess the images reconstructed and displayed on the Lexidata display system. Results indicate the approach could be utilized for acquisition of a test set suited to algorithm performance verification.

Initial study has suggested several possible improvements in components of both algorithms. For example, the usage of forward-and-backward frame-to-frame information should enhance overall robustness. Local edge detectors provide information used in the pseudo-probability function of the LDS algorithm and the cost function of the Modestino algorithm. Any improvements in the local detection of edges should yield improved performance for both algorithms.

Although the literature is extensive, the quantitative design and performance evaluation of local edge detection has received little attention. A new class of radially invariant, non-linear two-dimensional filters based upon a composite hypothesis testing was identified for study and development.

1. P. D. Clayton, L. D. Harris, S. R. Rumel, and H. R. Warner, "Left Ventricular Vidiometry," Computers and Biomedical Research, vol. 7, pp. 369-379, 1974.

2. J. W. Modestino, G. P. Ashkar, R. W. Fries, and H. Kaufman, "Computer Evaluation of Dynamic Left Ventricular Volume from Serial Angiocardiograms," Computers in Cardiology, IEEE Catalog No. 76CH1160-1C, pp. 211-218, 1976.

C. Systems for Pathophysiologic Studies

BCL activities addressing pathophysiologic studies began in 1970 when a minicomputer-based patient monitoring system was developed to aid in understanding and improving the postoperative management of cardiothoracic surgical patients. The prototype monitoring system used for seven years in Barnes Hospital demonstrated the value of on-line digital processing to clinical investigators, and the computer has since become a commonplace and valuable tool in many biomedical research activities. The increasing demands for digital computing have encouraged us to develop more flexible and enduring solutions to better satisfy pathophysiologic research needs. The Clinical Physiologic Research System (CPRS) offers a generalized approach to meeting a significant class of such needs with modular system elements and distributed processing. In addition to providing a method for implementing instrumentation systems in a local environment, the CPRS approach provides a convenient means for interfacing local instrumentation systems to more global networks where expanded computational and storage capacity reside.

During the past year, research activities have dealt with the development of instrumentation systems and measurement techniques for pathophysiologic studies in ophthalmology and cardiac electrophysiology. Included in these activities were the design and implementation of a system for acquiring multiple epicardial and endocardial electrograms from the left ventricle of acute canine preparations. An objective of this study is to measure patterns of local ventricular activation during repeated coronary occlusions. The feasibility of adapting this existing system to include chronic experiments of prolonged duration is currently being accessed. Collaboration between the Department of Ophthalmology and BCL has resulted in the development of an acquisition system for achromatic visual-field data. Automatic feature extraction algorithms have been created to process these visual-field records and to provide early detection of the visual-field defects associated with glaucoma. Work was begun on a color display system for mapping the spatial distribution of defects in chromatic visual function. Another system has been designed and is being used to study the dynamics of the fluid inflow and outflow mechanisms which control intraocular pressure.

C-1. Clinical Physiologic Research System

Personnel: R. W. Hagen, BCL

Support: RR 00396

The Clinical Physiologic Research System (CPRS) is a tool which has been used in several laboratory and clinical research applications to provide data acquisition, feature extraction, control, information storage and/or information display. The system employs a distributed and modular architecture which spans hardware, software and packaging. The identification of relatively independent tasks that can be performed asynchronously is an important first step in the application of the CPRS. Each independent task is usually implemented in a separate module and intermodule communications is accomplished through an IEEE standard-488 digital interface.

During the past year, the CPRS has been applied in the two research activities described in C-6 and F-4. These activities have used the CPRS for a variety of functions including user interface, signal sampling, information storage and microscope stage control. User interface functions have been implemented by programming a commercially available personal computer (Commodore PET). Another user interface function, tailored to a particular application, has been developed with a special hardware configuration. Signal sampling tasks have been accomplished by reprogramming the previously designed signal processing modules (SPM). The Universal Storage Device (G-3) was modified to incorporate an IEEE-488 interface in order to provide for information storage. A microscope stage control function was implemented using CPRS packaging and software modules.

To expedite the design and construction of CPRS modules, the wirelist system (G-8) has been expanded to accomodate the locally designed TM-500 wire wrap panel and a stock of these panels is maintained. Table 1 summarizes the CPRS hardware and software modules which have been implemented in conjunction with clinical and laboratory research activities at BCL. In addition to the locally designed modules, experience has been gained with the implementation of instrumentation systems which include commercial IEEE-488 compatible instruments.

hardware modules \ software modules	physiologic signal processing	IEEE-488 communication functions	general purpose mathematical	
data storage (DSM)		• electrogram acquisition		1.25 megabyte flexible disk drive and controller
signal processing (SPM)	• pulsatile perfusion • patient monitoring	• pulsatile perfusion • electrogram acquisition	• electrogram acquisition	A/D conversion digital I/O 4K bytes RAM
user interface (UIM)		• pulsatile perfusion	• pulsatile perfusion	programmable 32 character display and 8 function keys
signal generation (SGM)		• electrogram acquisition		D/A converter digital I/O 4K bytes RAM
IEEE-488 controller		• pulsatile perfusion		programmable IEEE-488 bus controller
microscope stage control		• silver grain measurement		controls X, Y, and focus of precision microscope
	QRS detection R-R interval systolic, diastolic, mean — pressure	implements IEEE-488 talker, listener, controller — functions in MC6800 chip set	trigonometric functions code conversions floating point higher precision	software module descriptions \ hardware module descriptions

Table 1. CPRS Hardware and Software Modules

C-2. Constant-Area Tonography System

Personnel: R. J. Arnzen, BCL
W. J. Grodzki, Jr., D.D.S., Ophthalmology
R. W. Hagen, BCL
R. A. Moses, M.D., Ophthalmology

Support: RR 00396
EY 00256

The purpose of the constant-area tonography system currently in use in the Barnes Hospital Ophthalmology Department is to study the dynamics of the inflow and outflow mechanisms which control intraocular pressure. The system allows measurement of the time course of intraocular pressure for a period of four minutes following displacement of a fixed volume of aqueous humor resulting from flattening and maintaining a constant diameter of contact between the cornea and a pressure transducer. Data obtained during the course of the experiment are recorded on a strip chart for immediate analysis and on a Universal Storage Device (G-3) floppy disk for subsequent computer processing. To date, no system failures have been encountered.

Data are being collected on patients with known intraocular pressure abnormalities as well as on normal eyes in order to provide a database from which statistically meaningful conclusions may be drawn. To date, 66 patients have been studied. Currently, the data are being analyzed and models proposed to explain the observed phenomena. Some of the initial analysis problems to be resolved are the separation of the arterial pressure component from the composite record obtained in these experiments as well as the component of pressure which may arise from muscular contraction during the measurement period.

C-3. Visual-Field Data Acquisition System

Personnel: R. K. Hartz, BCL
W. M. Hart, Jr., M.D., Ph.D., Ophthalmology

Support: RR 00396
EY 00336
EY 02044

During the past year, the M6800-based data acquisition system interfaced to a Goldmann perimeter in the Department of Ophthalmology has been in active use for patient examinations. The system has also been upgraded to include its use as a recording instrument during static perimetry. For this purpose, the perimeter has been modified to include a static fixation device for the pantographic arm and the software has been expanded and generalized

to include local floppy-disk storage of static-field results. Local communications between the data-acquisition system and the host minicomputer (PDP-11/34) have been generalized so that data may be transmitted to the minicomputer operating under either versions 3.1 or 3.2 of RSX-11.

C-4. Visual Fields and Ocular Hypertension

Personnel: W. M. Hart, Jr., M.D., Ph.D., Ophthalmology
R. K. Hartz, BCL

Support: RR 00396
EY 00336
EY 02044

The graphic database of visual-field records of patients being followed in the Glaucoma Center has been actively expanded during the past year. In addition to recording results of kinetic visual-field examinations, software has also been developed for storage and display of static visual-field results. Static perimetric data are now collected over two-dimensional areas of the visual field and the results are displayed, using a hidden-line algorithm, to construct a three-dimensional surface. In this manner, fine structural detail of central visual field defects, are graphically displayed as shown in Figure 1.

Automated feature-extraction algorithms for processing records of kinetic visual-field examinations, have been largely completed. These algorithms have now been incorporated into a generalized data-retrieval program, such that records may be searched for specific shape attributes, as well as for matches to demographic keys. The feature extraction algorithms are now being applied to analysis of the earliest detectable visual-field defects in a population of individuals who are known to have acquired glaucomatous defects while under observation at the Glaucoma Center over the past decade.

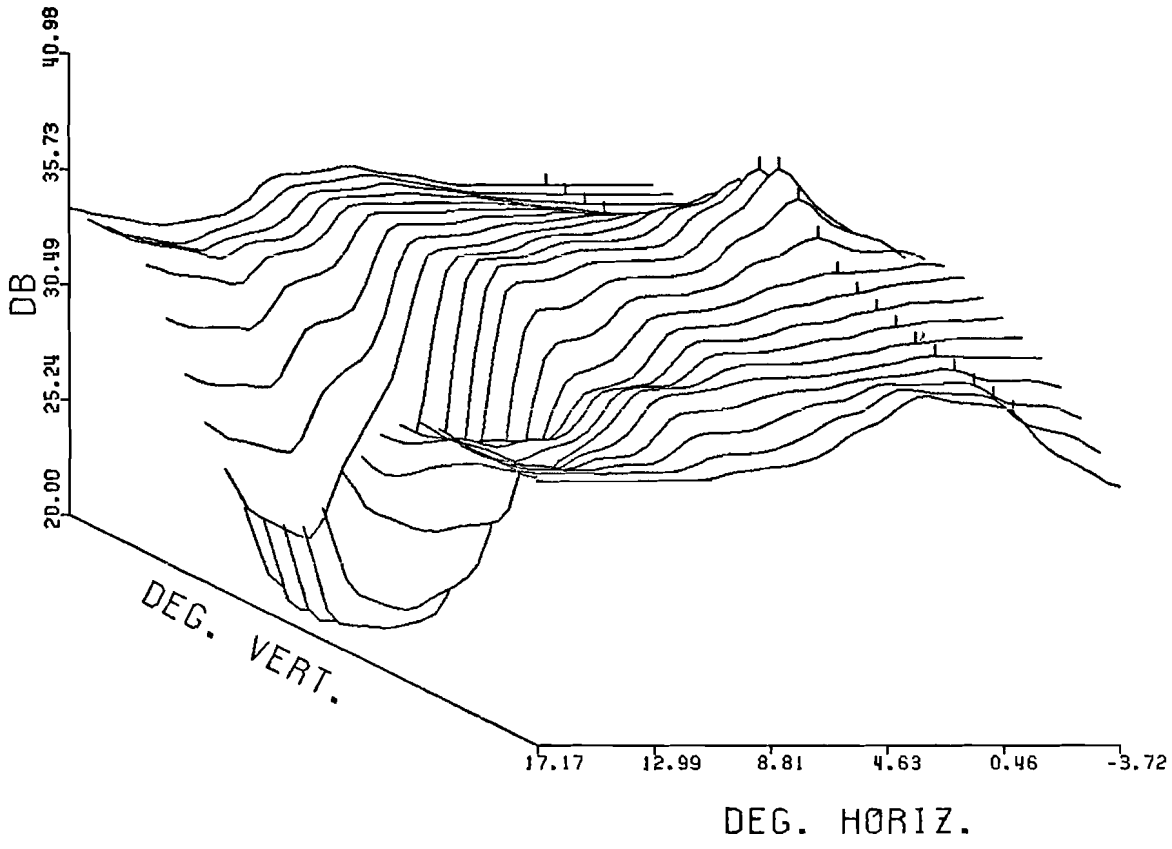


Figure 1. Three Dimensional Static Perimetry Display

C-5. Color-Perimetry Studies

Personnel: W. M. Hart, Jr., M.D., Ph.D., Ophthalmology
R. K. Hartz, BCL

Support: RR 00396
EY 00336
EY 02044

Work was initiated during the past year on the development of an M6800-based controller for a color video display to be used in color perimetry. Visual field examinations in the past, have been largely confined to mapping visual thresholds with target background lights that depend on brightness differentials. The use of colored lights as either targets or backgrounds has, in the past, met with limited success in the clinical setting, due to conflicts in determinations of thresholds that are based on color perception versus those that are largely determined by brightness differences. The visual system can make a true physiological distinction between perceptions of brightness, versus those of color per se (hue or saturation). Therefore, for color perimetry to be helpful, a technique must be devised to isolate the color properties of the visual target, while controlling its brightness differences with any background light.

Heterochromatic brightness matches, however, must be determined subjectively, and require the use of flicker photometric techniques. Because of this feature, and the fact that target and background lights must be mutually exclusive in space in order to independently control color and brightness attributes, it was felt that a video display system would be an ideal stimulus-presentation device.

An initial prototype display generator for a color television monitor has been constructed. This employs D-to-A converters for independently generating the voltage signals to each of the three primary phosphors of the video display screen (red, green and blue). Target-background pattern combinations are generated, consisting of diffusely illuminated backgrounds with a square or rectangular target which can be varied in size, shape, and position. In addition, target presentation is controllable either manually, or automatically in a flicker mode. Flicker rates, dictated by the 60-Hertz scan rate of the monitor, can be preset at 30, 15, or 7.5 Hertz. A manual potentiometer can be used to selectively vary the voltage to one or more of the phosphors within the target area during the flicker presentation.

The instrument has initially been calibrated in arbitrary units, using a photomultiplier detector, and initial experiments have been run to determine flicker photometric brightness matches between targets of varying colors and neutral-gray backgrounds of fixed levels of brightness. These experiments have confirmed that brightness matches can be obtained that are additive at varying levels of saturation of target color.

The greatest problem thus far encountered in the initial development of this instrument has been in the calibration of the light output of the video monitor. Brightness response of the phosphors, as a function of input voltage is highly nonlinear, and varies markedly with any variation in convergence and calibration contrast setting of the instrument. Consequently, a brightness recalibration technique must be developed that employs a feedback loop from a detecting photometer placed in front of the instrument.

C-6. Data Acquisition System for Extracellular Cardiac Potentials

Personnel: B. H. Tanaka, BCL
G. J. Blaine, BCL
R. W. Hagen, BCL
B. R. Hieb, M.D., Jewish Hospital
R. Ruffy, M.D., Jewish Hospital
C. D. Shum, BCL

Support: RR 00396
American Heart Association, Missouri Affiliate, Inc.
Buder Peters Scholar Award

Coronary artery occlusions produce substantial changes in the amplitude, duration and shape of left ventricular electrograms. Several acute canine experiments have been performed to investigate the repeatability of these ischemia-induced changes as a function of time for consecutive periods of occlusion. During two-minute and five-minute occlusive periods, multiple epicardial and endocardial electrograms are acquired using a data acquisition system that was designed around the modular Clinical Physiologic Research System architecture (C-1). The data acquisition system includes eight signal-processing modules (SPM), a user-interface module (UIM) and a data-storage module (DSM). The UIM programs the sampling sequence in each SPM by specifying sampling rate (20 to 20,000 sps), delay after trigger (1 to 200 milliseconds), and sampling window size (1 to 100 milliseconds). The sampling sequence in each SPM is initiated by UIM synchronous with cardiac stimulation. Each SPM stores digitized electrogram samples in an internal memory until the data can be transferred to the DSM.

A small personal computer (the Commodore "PET") was selected as the UIM. The capability to program in BASIC and assembler code, the use of the CRT display for prompting and protocol specification, an IEEE-488 interface, availability, and low cost were considerations in this selection. The user-interface function was implemented in BASIC. To specify sampling protocol, the user chooses from a menu and keys in appropriate responses. Use of the screen-editing and cursor-control capabilities of the PET result in an efficient interaction with system users by eliminating redundant tasks in the protocol-specification procedure. The IEEE-488 control functions are implemented within the PET in assembler code to overcome timing constraints

and deficiencies in the PET's pseudo-IEEE-488 interface. After the sampling protocol is specified, the BASIC program jumps to assembler code and the PET enters the control mode. In the control mode, the PET checks for a cardiac stimulation pulse. When a valid pulse is detected, the PET synchronously initiates the specified sampling sequence in each SPM. Once the sampling process is completed, the PET supervises the transfer of data from each SPM to the DSM for storage on a floppy diskette. The acquired electrogram data are transported via the floppy diskettes to a minicomputer system for off-line feature extraction and analysis.

The DSM is based on the Universal Storage Device (G-3) with an IEEE-488 interface port added. The use of tight assembler-code routines to communicate through the interface and the interleaving of sectors results in a worst-case data-transfer rate of greater than ten thousand bytes per second. The storage capacity of the double sided/double density diskettes (1.25 Mbytes) is proving to be insufficient for certain experimental protocols. We are examining the possibility of changing the present DSM to take advantage of the Winchester disk technology. Work continues on a signal-generation module (SGM) capable of displaying any two of the sixteen sampled electrograms on an oscilloscope. This module has been designed and construction is in progress. Display, refresh and communication routines are being written. Work is also being done to update and modify the routines in the UIM and DSM to enhance error checking and debugging capabilities and to include changes that were suggested by the data acquisition system users.

C-7. Preliminary Studies for Chronic Cardiac Experiments in Dogs

Personnel: B. R. Hieb, M.D., Jewish Hospital
G. J. Blaine, BCL
R. W. Hagen, BCL
R. Ruffy, M.D., Jewish Hospital
B. H. Tanaka, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
American Heart Association, Missouri Affilitate, Inc.
Buder Peters Scholar Award

A data acquisition system for signals generated during acute canine electrophysiologic experiments has been developed (C-6). The system acquires data from multiple bipolar electrogram probes for short periods. We are investigating the feasibility of adapting this system to chronic canine experiments extending over prolonged periods of time. The proposed chronic electrophysiologic data acquisition system (CEDAS) must be capable of handling electrophysiologic recording episodes extending over periods of months. In addition to acquiring electrophysiologic signals, the CEDAS system must

be able to process the outputs of transducers measuring other parameters including pressure, cardiac mechanical activity, potassium ion concentration, and neural activity.

In order to define the requirements for the CEDAS system, we have performed studies on the data acquired during the acute experiments. Specifications for electrogram signal data analysis have been established and work is proceeding on an an automated system for electrogram analysis. The different types of electrogram signals are being analyzed to provide information on the frequency content of each.

A survey of both implantable and external telemetry units was conducted to determine the practicality of using a radio-telemetry link for transmitting data from chronically instrumented dogs to a data acquisition system. This survey showed that neither experimental nor commercially available systems currently meet the needs of the proposed study. Telemetry systems which are compatible with these needs in terms of size and power consumption have insufficient bandwidth. Other researchers with similar needs have successfully used flexible, lightweight cables to provide a simple and versatile solution. Therefore, it was decided to utilize a tethered dog with a cable for the initial system configuration. The potential benefits of various data-compression schemes for data storage, data analysis and data transmission requirements are being evaluated. Preliminary studies examining the effects of autonomic neural stimulation on electrophysiologic parameters have been performed in the animal laboratory. An evaluation of methods for measuring and recording autonomic neural signals in both acute and chronic preparations is planned.

D. Databases for Disease Management and Research

The need for database facilities in several BCL projects became compelling in the early 1970s. Prior experience underscored the desirability of interactive data entry in order to assure adequate quality and to provide easy access to up-to-date information. Primarily through external funding, a minicomputer-based system (MUMPS) capable of supporting database activities was imported, rewritten for the PC-1200, and applied in radiation oncology. This application has developed into an installation, the Oncology Data Center (ODC), located within the Mallinckrodt Institute of Radiology. A fee-for-service installation, the Medical Computing Facilities (MCF), was organized within the Medical School to provide MUMPS service to those who do not desire to operate their own installations. BCL, itself, operated a MUMPS facility for training purposes and investigation into database characteristics until 1978.

In the previous year the Medical Computing Services Group (MCSG) was defined as a new activity of the Computing Facilities to serve the Medical School campus. MCSG provides a broad spectrum of facilities and services in order to assist researchers with data-management requirements. MCSG, which was established officially on July 1, 1980, supports access to both MCF's MUMPS system and to the University's IBM System/360-370.

Current activity in the Laboratory includes the development and operation of several information systems for the support of ongoing research projects. Almost all of these databases concentrate on chronic diseases because of the importance of a long-term database to clinical investigators studying long-standing illnesses. The emphasis of the database projects has shifted from the development and operation of several databases to the development, operation, and study of one database (D-5) and its related special-study files. Two of the Laboratory's databases, MIPI (D-2) and PIM (D-3), have been terminated; MCSG will serve as a resource in addition to MCF for the development of such databases in the future. The Laboratory will continue to concentrate on the development and operation of the Neonatology Database and its related files in conjunction with the goals of the Information Systems Group (D-1).

Following the long-standing tradition of the laboratory, an increasing emphasis has been placed on allocating the appropriate computer resource to each information-processing task. As the databases that are described in this section mature their analyses become of increasing importance. Because of the richness of the software development and because of the overall suitability of a general-purpose large-scale computer for analysis tasks, these have been performed largely on the University's IBM System/360-370. SAS, a popular statistical-analysis/data-management package, has provided the primary vehicle for the analyses of databases originally managed on other computing systems.

Experiences with disparate applications and with the instrumentation of conventional information systems continue to benefit design activities. Development activities directed toward a high-performance information system capable of smooth growth have been federated within the Information Systems Group, a sister Resource group based in the Computer Science Department.

D-1. Information Systems Group

Personnel: J. R. Cox, Jr., Computer Science, BCL, and Computer Systems Lab
G. J. Blaine, BCL
M. W. Browder, BCL
R. E. Hitchens, BCL
M. M. Maurer, Jr., BCL
P. Moore, BCL
S. R. Phillips, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HS 03792
Washington University

The Information Systems Group provides the collaborative structure within which participants from the Department of Computer Science, the Department of Electrical Engineering, the School of Medicine, and the Biomedical Computer Laboratory are addressing the development of a methodology for the design of composite medical-information systems. The development activities encompass specification of an abstract model for a database system, design and implementation of software modules for a generalized medical-information system, operation and analysis of a database designed for clinical research, performance modeling and evaluation, and architectural design studies based on VLSI-design techniques.

The tightly knit interdisciplinary team ensures an environment based on direct experience with the operation of a complex medical-information system which contains data on real patients and which is used by real decision-makers to facilitate realistic model development and architectural considerations.

Primary emphasis and progress during the past year is related to development of the abstract database model; studies of a relational database system designed for the PDP-11; operation, enhancement, and analysis of the Neonatology Database (D-5); and initiation of VLSI-design studies for a name-searching processor unit which was recognized as an important kernel for implementation based on the model. Specific details of these activities are summarized elsewhere.[1]

1. "A Medical Information Systems Design Methodology," HS 03792-02 Continuation Application, J. R. Cox, Jr., June 1980.

D-2. Myocardial-Infarction Patient-Information (MIPI) Database

Personnel: P. Moore, BCL
L. L. Brandenburger, BCL
K. W. Clark, BCL
E. M. Friedman, BCL
J. R. Humphrey, R.N., Jewish Hospital
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
J. P. Miller, BCL
G. C. Oliver, M.D., Medicine
C. J. O'Rourke, BCL
M. A. Province, BCL
R. Roberts, M.D., Medicine
S. Thanavaro, M.D., Jewish Hospital
E. Thornton, BCL
P. T. Wallace, Jewish Hospital

Support: RR 00396
HL 18808
Barnes Hospital
Jewish Hospital
Washington University

The Myocardial Infarction Patient Information (MIPI) system (PR 12, A-1; PR 13, D-2, PR 14, D-2; PR 15, D-2) provided data management for the Sudden-Death Study. During the past year, the system has ceased to function since all data were passed to a SAS database (PR 15, D-10) and the project has entered the statistical-analysis phase. Generalized routines have been retained to support future activities and they have aided in the development of other databases.

The gathering and management of data for the study can be classified into three categories: 1) the recording of Coronary-Care-Unit (CCU) admissions for Barnes- and Jewish-Hospital patients (10/27/75 - 03/31/78) and the gathering of relevant clinical data for all myocardial-infarction (MI) cases, 2) the scheduling of ambulatory-ECG recordings and the acquisition of related data elements, and 3) the follow-up done on all surviving MI patients.

All patients admitted to the Barnes CCU or Jewish Medical Intensive-Care Unit were initiated in the system via a registry-enrollment form, and then, depending upon the admitting and final diagnoses, the system controlled the entry of data relevant to the in-hospital phase of the study. The major emphasis of the data-collection process was on patients diagnosed as definite MIs. The CCU stays of these patients were documented and an attempt was made to recruit those surviving their CCU stay into the monitoring program. For patients recruited into the monitoring program, two recordings were made. The first recording was made 10 to 14 days post-MI, followed by another 2 to 3 months post-MI. Thereafter, the recordings were continued for qualifying patients at three-month intervals for a minimum of one year. The MIPI system noted patients to be scheduled,

generated applicable correspondence, and handled the diverse sources of data related to each recording. All surviving MI patients were followed at six-month intervals to document their post-MI status. The MIPI system aided the follow-up process by providing appropriate lists and correspondence.

During the past year, the MIPI system has supported four final study-management activities. The following of all surviving MI patients has been completed; thus, the status of most patients as of March 1, 1979 is known. Final results for 19 of 1152 Study I cases and 9 of 1079 Study II cases could not be obtained. All of these results have been sent to the SAS database. The protocol under which the measurement of CK values was made was established, the values were keyed and then sent to the SAS database. The 12-lead ECG data, which were collected in connection with the ambulatory-ECG monitoring, were checked extensively and also passed to the SAS database. Finally, the contents of the SAS database were verified using a record index created by the MIPI system.

The MIPI system has aided project personnel both in the collection of data and its conversion to codes. Because the system guides the user through the entry procedure and flags errors immediately, the number of errors due to omissions has been few. This application has confirmed the benefits of a study-management strategy that separated the protocol-management and statistical-analysis functions.

D-3. Protection of Ischemic Myocardium (PIM) Database

Personnel: P. Moore, BCL
M. Bland, R.N., St. Louis University
L. L. Brandenburger, BCL
A. E. Dyer, R.N., St. Louis University
R. G. Evans, B.A., St. Louis University
E. M. Friedman, Biostatistics
S. A. Kaiser, R.N., St. Louis University
J. P. Miller, Biostatistics
H. S. Mueller, M.D., St. Louis University

Support: HV 62960
St. Louis University

The MUMPS-based Protection of Ischemic Myocardium (PIM) system (PR 13, D-3; PR 14, D-3; PR 15, D-3) coordinated the double-blind propranolol-intervention study for the reduction of myocardial-infarct (MI) size run by St. Louis University and two collaborating institutions, St. John's Mercy Medical Center and the Veterans Administration. During the past year, the system has ceased to function since all data were passed to a SAS database (PR 15, D-10) and the project has entered the statistical-analysis phase. Generalized routines have been retained to support future activities and have aided in the development of other databases.

The data-collection protocol for this study is complex. From each of three institutions, data are collected concerning the hospitalization and especially the Coronary-Care-Unit (CCU) stay of any patient admitted with a diagnosis of rule out MI. The designation of which forms are to be completed is determined by the patient's classification: 1) recruited for study, 2) eligible but not recruited, 3) not eligible but MI was diagnosed, or 4) not eligible and no diagnosis of MI.

The major thrust of the system revolves around recruited patients for whom a minimum of sixty-five forms are completed. Besides data similar to those obtained by the Myocardial-Infarction Patient-Information (MIPI) system (D-2), hemodynamic measurements are made for 72 hours, metabolic measurements for 4 days, propranolol blood levels for 10 days, and creatine-kinase measurements for a maximum of 126 hours. Thallium-201, technecium-99m-labeled stanous pyrophosphate, and labeled human-serum albumin (HSA) scans are made at various scheduled intervals during the hospital stay. Additionally, six Holter recordings are taken. All medications administered during the first 14 days of the hospital stay are recorded with a code number indicating the reason for administration and the dosage. Any significant events occurring during that time are noted by time of occurrence and by a numerical code. Recruited patients are scheduled for follow-up visits at 3, 6, and 12 months post-MI, at which time five procedures are done (stress test, HSA scan, electrocardiograph (ECG), ambulatory-ECG recording, and chest X ray) and a follow-up form is completed.

During the past year, the PIM system has supported final study-management activities for the project. The enrollment of patients was terminated March 31, 1979. Data for all patients were entered and checked by September 1, 1979. These checks included cross-matching responses on various forms. All free-text data were then converted to codes. In-hospital data on all patients and data concerning most outpatient visits were sent to the SAS database by October 1, 1979. Then the system was deactivated. In April, 1980 the PIM system was reactivated for an additional month in order to process the data accrued on outpatient visits that took place after October 1, 1979.

This application reinforced our belief in emphasizing study management and allowed us to incorporate additional features in the evolving protocol-management system. More checks were applied through table-driven routines rather than as special cases and checks were done on items within and among forms. Incorporating these consistency checks at the inception of the study improved data quality. Additional checks were incorporated as new relations among items were defined. This application also required better protocol-adherance skills because much attention was directed toward the proper completion of the patient's recruitment form, the correct assignment of a patient's category, and the inclusion of all data items required by the protocol.

Appropriate coding lists have been retained from this application. Three particularly useful items of cardiologic data are a list of typical medications along with expected dosages and schedules, a list of CCU occurrences and a list of complications after CCU discharge.

D-4. SCOR Patient Information Database

Personnel: K. B. Schechtman, BCL
H. D. Ambos, BCL
E. Gaelig, R.N., Medicine
E. M. Geltman, M.D., Medicine
A. S. Jaffee, M.D., Medicine
J. Markham, BCL
A. T. Marmor, M.D., Medicine
R. Roberts, M.D., Medicine
B. E. Sobel, M.D., Medicine

Support: RR 00396
HL 17646

The Specialized Center of Research (SCOR) database (PR 15, D-4) currently contains information pertinent to 602 patients who have suffered acute myocardial infarction. The variables contained therein describe the patients' cardiovascular history, in-hospital physical condition, and long-term progress as assessed through follow-up examinations. During the year immediately after each index coronary episode, the progress of each patient is assessed at three-month intervals. Follow-up interviews are then continued on a yearly basis. The data records are entered onto disk using the Interdata computer in the Coronary Care Unit and then transferred via magnetic tape to the IBM System/360-370 at the University's Computing Facilities. There, a permanent SAS database is maintained for analysis of the results of a variety of clinical studies.

The SAS database consists of about 240 variables, resulting in about 2800 data items because measurements of some variables can be obtained up to 21 times during the patient's hospital stay. The database is maintained on seven separate tape files. These contain information on patient history, daily clinical status, serum enzymes and blood chemistry, hemodynamic parameters, dynamic ECG recordings and cardiac-output reports, graphic measurements, and follow-up data. Those variables that are required for a particular clinical investigation are copied from the tape files and merged into a single disk file in order to expedite statistical analysis utilizing the IBM System/360-370 computer.

Patients with diabetes mellitus have been reported to have a high incidence of congestive heart failure and cardiogenic shock in association with acute myocardial infarction. Since in addition to their coronary artery disease, such patients may suffer autonomic dysfunction, renal failure, or cardiomyopathy, the relative contribution of these abnormalities to the production of congestive heart failure and/or cardiogenic shock is unclear. In order to clarify these issues, a comparison of diabetics and non-diabetics with respect to several variables in the SCOR database is being performed. A subset of patients without a history of previous infarction is being evaluated as well.

Male diabetics were of approximately the same age and have infarct sizes similar to those in controls. However, female diabetics were significantly younger and had smaller infarcts than their non-diabetic counterparts. At the .01 level of significance, diabetics had a higher incidence of pulmonary congestion as well as higher clinical (MIRU) class. Surprisingly, diabetics with myocardial infarction comparable to controls had consistently fewer and less complex PVCs than non-diabetics.

A total of 200 patients with acute myocardial infarction have been studied for at least 14 days after onset in order to determine those factors which predispose an individual to a repeat infarction during the initial hospitalization. The association between repeat infarction and 10 dichotomous and 2 continuous variables were examined. Those which proved significant were infarct location ($p = .0001$), recurrent chest pain prior to the recurrent infarction ($p = .0001$), gender ($p = .0040$) and obesity ($p = .0241$). Although only 18% (35/200) of the overall group suffered recurrent infarction, 43% of the patients with subendocardial infarction, compared to 8% of those with transmural infarction, exhibited early recurrence. Forty-one percent of those with at least three episodes of prolonged recurrent chest pain antedating suspected recurrent infarction exhibited recurrence compared to 5% of those without such pain. Women were more likely than men (29% compared to 12.3%) and obese patients more likely than non-obese patients (28% compared to 14%) to exhibit recurrent infarction. These results identify a subset of patients at high risk for recurrent infarction requiring appropriate prophylactic interventions. This subset will be evaluated objectively in ongoing studies.

D-5. Neonatal Database

Personnel: P. Moore, BCL
L. L. Brandenburger, BCL
M. M. Buckley, Pediatrics
R. E. Marshall, M.D., Pediatrics
M. M. Maurer, Jr., BCL
J. L. Roberts, M.D., Pediatrics
S. M. Scott, M.D., Pediatrics
E. Thornton, BCL

Support: RR 00396
HS 03792
St. Louis Children's Hospital

Day-to-day clinical experience with sick newborns stimulates many questions based on historical, clinical, and/or laboratory data. The Neonatology Database (PR 12, D-16; PR 13, D-5; PR 14, D-5; PR 15, D-5) was designed to allow the easy formulation of queries and their rapid response. Data are collected on all admissions to the Newborn Intensive-Care Unit (NICU) of St. Louis Children's Hospital. Admission data, including

maternal history, perinatal history, immediate post-delivery data, and initial admission evaluation are gathered soon after an infant's admission. For in-hospital data, the onset and termination dates (if known) of occurrences are noted and relationships among objects are encoded with a problem/concurrent-event/complication approach. In order to summarize the entire hospital stay, codings are made under 23 broad categories which encompass organ systems, diseases, laboratory values, therapies, procedures, and other events of interest. Exact laboratory data are entered for patients of special interest.

The system provides a useful means of evaluating relationships via tabulation and simple statistics and allows for growth both in number and type of data. A generalized format has been provided so the system's features can be transferred to other medical contexts and one special study on premature infants is being established (D-7).

This MUMPS-based database has existed on three separate computer systems since its inception in June 1975. The database was first developed on an Artronix PC-1200 system as a pilot study to determine coding strategies. The relative stabilization of encoding techniques coincided with the decision to transfer to an Artronix MODULEX system in June 1977. Since the data collected had varied, the features of the system were transferred but the data were not retained.

In June 1979, the demise of Artronix, Inc. and consequent operational problems with the MODULEX system resulted in the decision to transfer the 953-patient database to a TANDEM system operated by the Pathology Department of St. Louis University. Since bit functions did not exist in this version of MUMPS, the development of a different search method to achieve rapid retrieval was devised. The entire system was regenerated in six weeks in order to satisfy demanding needs for information. All programs were recoded because of the new searching technique, because of improvements made to all file designs, and because of other system enhancements.

The alternate searching method was satisfactory for temporary use, but it was unacceptable for long-term use since excessive disk space was required for the inverted file, search times varied greatly, and the more demanding searches degraded overall system performance. The author of the local MUMPS interpreter was persuaded to incorporate bit functions, the system was redone, and a comparison of the two methods was made. Required disk storage decreased, search times and overall system performance improved, and coding for quick retrievals was less obscure. The amount of time dedicated to these changes was substantial but the quality of the system improved with each overhaul.

The system has been stable since December 1979 and new software has been developed to extend its use. Appropriate changes have been made in preparation for quick searches of in-hospital data where elements of time such as duration, precedence, or offset are included. Programs dealing with time-oriented queries are in preparation. Greater attention has been paid to data checking and unique checks have been identified. Many of these checks are defined by users through the system's software.

In addition to the experience gained and clinical research done with the Neonatology Database, it serves as a tool for modeling medical-information structures and for studying users' needs. The system has been instrumented so that all queries are logged in an on-line file to characterize usage. Several preliminary studies have used the database to examine data relations in medical information and to check various iterations of the database model. The "recognizer" concept has been examined in terms of admission data and the definitions used to encode in-hospital data were studied to determine where they could be computerized. The interactions of in-hospital items have been characterized and a classification scheme is being devised to identify each term's "type." Interim tabulations based on these categorizations have accentuated the variety of types and relations present in medical data. These efforts have emphasized both improving data quality and categorizing various types of expressions that connote relationships having medical implications.

The patient population has finally become sufficiently large to entice a variety of users. There are 1800 patients in the database and 1228 have in-hospital data entered. Plans now center on the development of an active user community and on increasing the number of patients with in-hospital data complete.

D-6. Methodological and Technical Developments for Risk-Function Analysis

Personnel: J. P. Miller, BCL and Biostatistics
E. M. Friedman, BCL and Biostatistics
J. Y. Lee, Ph.D., Biostatistics
M. A. Province, BCL and Biostatistics
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 18808
HV 62960
Washington University

The development of statistical models for assessing the probability of some future event, such as death, given a set of data for a patient, is of continuing interest for the analysis of data obtained on chronic diseases. During previous years efforts were directed towards implementing software to evaluate several statistical models for risk-function analysis (PR 13, D-18; PR 14, D-13; PR 15, D-11). During the current year these models were applied to the analysis of the natural history of sudden death (A-7).

The in-hospital morbidity and mortality of nontransmural and transmural myocardial infarction (MI) were compared in patients hospitalized with their first infarction. Log-linear analyses indicated that when patients

were stratified by the peak level of SGOT, the type of infarct did not contribute to the assessment of risk of mortality and morbidity.[1,2]

In studying long-term mortality we examined 610 patients who had survived their hosptialization.[3] During the first year, and especially during the first six months, the clinical features of the acute event, especially those reflective of the extent of the infarct, but not of the type of infarct, were powerful predictors. We were able to determine that the ratio of the failure rates of transmural and nontransmural infarcts did not remain constant over the three year follow-up period. This indicates a violation of the Cox proportional hazard model,[4] and forced our analyses to be repeated for varying time periods, e.g., 0 to 1 year post-MI, 1 to 2 years post-MI, 2 to 3 years post-MI. These analyses indicated that as the MI became more remote, the utility of the features observed during the acute event decreased. In fact, for some of these features the direction of their influence was reversed. Thus, in the 2- to 3-year period, patients who had suffered a nontransmural infarct appeared to be at greater risk than those with transmural infarcts, a reversal of the first-year result. These findings, if replicated, call into question the prevalent practice of utilizing in an uncritical manner the Cox model for evaluating the long-term prognosis of patients following their MI.

Analyses of the relationships between events observed during the acute MI and subsequent runs of premature ventricular contractions (PVCs) observed using Holter monitoring during the year following the infarct indicated that severe cardiac disease made manifest by poor left-ventricular function, high serum-enzyme levels, and certain types of cardiac arrhythmias, are associated with an increased prevalence of ventricular runs during the post-hospital phase.[5] Utilizing a multivariate logistic function, we found it possible to divide the patients into quartiles of risk with the prevalence of runs ranging from 4% in the lowest quartile to 49% in the highest one. Although the rate of sudden death was not different in each quartile, patients in the highest quartile had significantly higher rate of death from all causes, suggesting that the increased mortality was related to severe cardiac disease rather than to the presence of the PVC runs themselves.

1. S. Thanavaro, R. J. Krone, R. E. Kleiger, M. A. Province, J. P. Miller, V. R. deMello, and G. C. Oliver, "In-hospital Prognosis of Patients with First Nontransmural and Transmural Infarctions," Circulation, vol. 61, pp. 29-33, 1980.

2. S. Thanavaro, R. J. Krone, R. E. Kleiger, M. A. Province, J. P. Miller, V. R. deMello, and G. C. Oliver, "In-hospital Prognosis of Patients with First Nontransmural and Transmural Infarctions," International Congress Series No. 491, Florence International Meeting on Myocardial Infarction, Excerpta Medica, Princeton, pp. 100-102, 1979.

3. R. J. Krone, E. M. Friedman, S. Thanavaro, J. P. Miller, R. E. Kleiger, and G. C. Oliver, "Long-Term Prognosis of Patients with First Transmural and Nontransmural Myocardial Infarction," accepted for presentation at the 1980 American Heart Association Meetings.

4. D. R. Cox, "Regression Models and Life Tables," Journal of the Royal Statistical Society, Series B, vol. 34, pp. 187-220, 1972.

5. R. E. Kleiger, J. P. Miller, S. Thanavaro, M. A. Province, T. F. Martin, and G. C. Oliver, "Relationship between Clinical Features of Acute Myocardial Infarction and Ventricular Runs Two Weeks to One Year Following Infarction," Circulation, in press.

D-7. Mineral-Homeostasis and Mineralization Database

Personnel: P. Moore, BCL
L. S. Hillman, M.D., Pediatrics
L. A. Martin, CPNP, Pediatrics
M. M. Maurer, Jr., BCL
S. J. Salmons, PNP, Pediatrics

Support: HD 09998
HS 03792
St. Louis Children's Hospital

The Neonatology Database (D-5) provides a generalized format so that self-contained patient subsets can be established quickly in the database, a variety of tabulations and simple analyses can be performed, and data can be shared between files. One special file is serving as a test case. Dr. Laura Hillman is studying a subset of the neonatal population as well as additional patients treated at the Barnes Hospital Premature Nursery. These infants have been studied on a series of protocols to evaluate bone mineralization and calcium-phosphorous homeostasis.

Under the first protocol, 80 premature infants and 32 small-for-gestational-age (SGA) infants were serially studied at three-week intervals with X rays and chemistries. Daily intakes and weight gains as well as weekly lengths and head circumferences were recorded. Prenatal, neonatal, and hospital-course data were collected. Now, two new protocols for evaluating the effectiveness of therapeutic interventions are employed; these are designed to reverse abnormal calcium metabolism. The infants are followed in a special clinic where long-term follow-up data, including growth parameters, I.Q. testing, and dental evaluations, will be collected and added to the database.

Dr. Hillman's studies dealing with premature infants serve as a test case for this feature, and those involved with her project have found the new system easy to use. To date, the only problems have been entry of the backlog of patient data and the development of the desired types of statistical tests. Research laboratory data and admission data have been entered for a subset of her patients. Other data that remain to be entered include those related to intake, anthropometric, in-hospital

and follow-up information. The full value of this system will be realized when complete admission, in-hospital, and laboratory data have been entered for all infants included in this study.

Dr. Hillman's study has improved those components of the system dealing with data entry and analysis of quantitative data. The original Neonatology Database had emphasized the occurrences of coded data, whereas her primary concern to date has been with quantitative data. Adding features such as new time-frame calculations and statistical routines have improved the overall appeal of the system. Other features for analyzing both quantitative data and encoded data, for calculating derived parameters, and for searching and categorizing quantitative data will be incorporated.

D-8. Databases to Complement Ambulatory-ECG Tape Processing

Personnel: P. Moore, BCL
K. W. Clark, BCL
K. A. Madden, BCL
J. P. Miller, BCL
M. A. Province, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
HL 22982
HV 72941
Barnes Hospital
Jewish Hospital
St. Luke's Hospital East
Washington University

Protocol-management systems monitor the analysis of ambulatory-ECG recordings which are done for the MILIS (A-21) and MPIP (A-19) studies. Data are keyed into these management databases and checked as steps in the protocol are completed. In this way, the system tracks the progress of each recording analyzed. The data include appropriate dates; thus, the completion date of each event in the protocol is recorded. Also entered is information concerning the arrhythmic content of each recording as determined by automatic analysis, editing, and cardiologic review. The protocol-management systems assist local activities by allowing a user to retrieve data on any recording, to determine the status of any recording, and to generate lists of recordings whose status in the protocol are similar. Three report generators allow retrospective studies of the analysis process and the definition of internal and external bottlenecks by noting the durations between events. User-specified searches including queries about durations can determine extreme cases.

These two databases were established and are maintained with relative ease since table-driven software from the MIPI (D-2) and PIM (D-3) systems

could be used. Data-checking and data-tracking features were quickly established to utilize this pre-existing software. Activity in the current year has concentrated on extending the reporting and searching capabilities of the system. These capabilities were added so that the local data manager could report general trends and document extreme cases.

The protocol-management system that supports recording analysis for the MILIS study is more extensive since patients are monitored three times and the results of Argus/2H analysis are stored in a statistical database. Since the BCL Holter Core Laboratory is notified of both patient registrations and terminations, the protocol-management system anticipates the receipt of recordings.

These two systems are in routine use, with 798 recordings presently noted in the MILIS database and 367 in the MPIP database.

E. Speech and Hearing

Early collaboration with Central Institute for the Deaf resulted in the development of digital instrumentation suited to speech-and-hearing research. The first systems that were developed, a Random-Access, Programmable (RAP-I) digital recorder, a computer system for processing sampled speech, and a RAP-II system that is interfaced to the LINC computer in the physiology laboratory, continue to be used in a variety of research applications, including the analysis of sampled speech sounds and glottal source waveforms and the synthesis and tailoring of speech sounds for psychoacoustic experiments with human and animal subjects.

The proven usefulness of these first systems has led to the development of newer RAP systems that can be programmed to accommodate a variety of psychoacoustic experiments and a central computer system with increased sampled data capability. This work is finished and laboratories at Central Institute for the Deaf have been renovated to accommodate these new systems.

More recently a major emphasis has been directed towards certain basic questions related to hearing and deafness, that require the digital instrumentation available through the collaboration. These areas of study include the following: 1) measurements of psychophysical characteristics of electrocutaneous stimulation to determine if this sensory modality can serve as a substitute input for speech for profoundly deaf patients, 2) the measurement of glottal source characteristics of normal and deaf talkers, 3) the development of methods for generating rapidly changing visual displays that can be used in lipreading studies, and 4) psychoacoustic studies related to questions of speech perception.

A major focus of the psychoacoustic studies is to understand the acoustic and neural transformations that are important in speech perception that occur in the cochlea and other parts of the auditory system. Towards this goal, we have studied, this year, the spectral characteristics of natural vowel sounds with a psychophysically-based model of hearing (E-6) and have undertaken a comprehensive study of proposed methods of vowel normalization to determine their relative merits (E-7, E-8). This work has suggested certain directions to be taken in theories of vowel perception (E-7).

E-1. Computer System for Auditory Research

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
R. Glaesner, Central Institute for the Deaf
M. T. Hakkinen, Central Institute for the Deaf
J. P. Tadlock, Central Institute for the Deaf

Support: RR 00396
NS 03856

The last of the RAP-III systems has been installed in the Psychoacoustics Laboratory. This system has been in general use for listening to and recording speech sounds and for engineering checkout and program development. The psychoacoustic installation includes four subject terminals, an 8-channel audio system with independently controllable attenuation, and an interface between the RAP-III system and a system of Grason-Stadler 1200 series logic.

A program has been written for this installation to do dichotic studies of auditory function. The program presents stimuli consisting of fragments of natural speech sounds, cues the subjects when a response is requested, scores the subjects response, and provides visual feedback as to the correctness of the response. Session parameters, number of subjects, stimuli, and trials, and stimulus duration can be specified by the experimenter. Response data are stored in separate disk files for each subject to facilitate data analysis at another time. Monaural identification trial types have been implemented first. The program is organized so that new trial types can be added without disrupting ongoing experiments.

The design of a RAP-IV system for the Signal Detection Laboratory at Central Institute for the Deaf has been completed and parts are on order. This system will eventually replace the aging PDP 8/I system currently in use. The RAP-IV system includes a NOVA 4-X computer with 256k bytes of memory, multiply/divide hardware, and a Model 8388 floating point unit and a set of RAP subsystems. The RAP subsystems include two Pertec 3400 series disk drives that can be used for program and data storage and that are compatible with other systems at CID and BCL, two 2-channel analog subsystems, and a laboratory station driver subsystem.

ALGOL subroutines have been developed to facilitate programming of the RAP-III systems for behavioral testing. These subroutines support RAP functions such as "record" and "play," the timing and I/O functions of the laboratory station driver, and a 4-channel serial interface. Programs are written using Data General's ALGOL 60 language which greatly reduces the time and complexity of program development and results in software that is easier to maintain and modify. The structured nature of the language lends itself to rapid implementation of most experimental procedures in addition to providing a common language for data analysis and system utility programs.

E-2. Speech Microscope

Personnel: N. R. Vemula, D.Sc., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf
J. L. Lauter, Ph.D., Central Institute for the Deaf
R. B. Monson, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

Two options have been added to the speech microscope program described in PR 15, E-2. The first one is a bandpass filtering option to compute the filtered signal corresponding to a specified speech segment. The user specifies the speech segment using the analysis-window-cursors and types in the lower and upper limits of the passband in the frequency region 0 Hz - 10 kHz. Then, the program computes the discrete Fourier transform of the specified segment and synthesizes the filtered signal using the amplitude and phase information of the harmonic components in the passband region.

The second option computes the center of gravity, expressed in Hz, of the discrete Fourier transform of a speech segment. Each spectral line is considered as a mass element located along the frequency axis, with its mass equal to the dB value of the line. The user again types in the lower and upper frequency limits between 0 Hz and 10 kHz, and the program determines the center of gravity of the specified spectral segment with an optional linear or logarithmic frequency scale.

We have also studied the accuracy of measurement of formant frequency using the linear predictor (LP) analysis option of speech microscope. These measurements are important in the study of speech production and form a basis for synthesis of speech. To assess the accuracy of formant estimating, vowels were synthesized with both a parallel and serial synthesizer model and a typical glottal source function. Parameters that are known to influence the accuracy of measurement such as fundamental frequency, formant bandwidth, and proximity of one formant to another were varied by synthesizing five different vowels (/i/, /æ/, /ɔ/, /r/, and /u/) that represent all of the extremes which can be encountered in vowels. The vowel /æ/ has widely spaced formants in approximately the middle of each formant frequency range. The vowels /i/ and /u/ represent the extremes of high and low first and second formants. The vowel /ɔ/ represents the case of close proximity of the first and second formants, while the vowel /r/ represents the case of the close proximity of the second and third formants. Tokens of these vowels were synthesized with ten different fundamental frequencies, from 100 to 500 Hz. In addition, tokens of the vowel /æ/ were also synthesized with four different bandwidths, 50, 100, 200, and 400 Hz.

These tokens were analyzed using the LP option and the results compared with the original values of synthesis. For tokens of fundamental frequency between 100 and 300 Hz, LP analysis estimates formant frequencies of parallel synthesis plus or minus 50-70 Hz; formants of serially synthesized tokens are estimated to within plus or minus 20-35 Hz. As might be expected, the accuracy of the formant frequency estimation deteriorates rapidly in the presence of (1) fundamental frequency higher than 350 Hz; (2) bandwidths wider than 100 Hz; and (3) close proximity of any two formants. The vowels used for this study represent the most difficult measurement cases, so that these estimates are undoubtedly the extremes. Natural speech probably falls somewhere between the parallel and serial types of synthesis.

E-3. Determination of Vocal Tract Shape During Phonation from Input/Output Measurements of Throat-Wall Vibration Near the Glottis and Sound Pressure at the Lips

Personnel: N. R. Vemula, D.Sc., Central Institute for the Deaf
D. L. Elliott, Ph.D., Systems Science and Mathematics
A. M. Engebretson, BCL and Central Institute for the Deaf

Support: RR 00396
NS 03856

Work has been completed on this project and a manuscript is currently in preparation.

As mentioned in PR 15, E-3, earlier attempts to obtain the vocal tract shape during phonation using the linear predictor (LP) procedure on the speech signal making some simple assumptions about the glottal source did not give consistent results, which prompted the present study.

It is hypothesized that the vibration on the neck near the glottis consists of two components: the "acoustic" component due to the supraglottal sound pressure and the "mechanical" component due to the force exerted by the vibrating vocal folds on the thyroid cartilage.

The acoustic transfer function characteristic of the throat-wall (relating the supraglottal pressure and the acoustic component of vibration) is experimentally determined by applying an external force on the neck with a vibrator and measuring the resulting inside response of the wall with a reflectionless terminator tube at the lips. During the experiment the subject held his glottis closed while holding a neutral tract shape. These measurements and a maximum likelihood, pole-zero model for the

wall have shown that the wall has a low-pass characteristic, falling off at about 10-12 dB/octave in the frequency region 90 Hz - 2 kHz.

A lumped-parameter mechanical model for the throat-wall was developed based upon the physiology of the larynx, existing data on the elastic properties of larnygeal muscles and ligaments, and also on measurements on scaled physical models for the larynx and subject's neck. The model agrees well with the above experimental measurements.

The throat-wall is considered as a 3-port network with "acoustic," "mechanical" and "output" ports, corresponding to the supraglottal pressure excitation, mechanical excitation by the vocal folds and vibration measurement on the neck, respectively. One element of the 3×3 symmetric network matrix corresponds to the measured acoustic transfer function of the wall. A second element, corresponding to the driving point impedance at the output port, is measured by applying a mechanical force on the neck with the vibrator and measuring the resulting vibration of the outside surface of the neck. The remaining 4 unknown elements are evaluated using a computer simulation of the above mechanical model.

Fourier analysis of the simultaneous measurements of the pressure on the inside surface of the wall and external vibration on the neck while the subject phonates into the terminator tube holding a neutral tract shape has shown that the transfer function characteristic of the wall relating the inside pressure and the external (total) vibration varies within -7 to -10 dB from that at normal pitch and intensity. On the other hand, repeated measurements at normal pitch and intensity have indicated a comparable variation in the measurement of the vibration, probably due to the variation of the compliance of the skin on the neck. Not inconsistent with these facts, the wall is modeled as a linear, pole-zero model, the parameters of which are evaluated using a maximum likelihood scheme. This model is used in determining the vocal tract shape.

Simultaneous measurements of the sound pressure at the lips and the vibration on the neck are made for vowel phonation at normal pitch and intensity. An approximation to the glottal source signal is determined from the measured vibration. The vocal tract shape is determined using an all-pole model for the tract. To compare the input/output and linear predictor procedures two experiments are performed. In the first experiment measurements are made with and without a tongue hump made at the lip-end of the subject's tract. In the second experiment, measurements are taken with and without a cylindrical wooden piece of known dimensions placed within the tract. Comparison indicates that the input/output procedure gives more consistent results than the linear predictor procedure. It is also shown that the input/output procedure gives reasonable tract shapes for vowel phonation.

This work comprises Vemula's D.Sc. dissertation, Department of Control Systems Science and Engineering, Washington University.

E-4. Voice Source Characteristics

Personnel: R. B. Monsen, Ph.D., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf
N. R. Vemula, D.Sc., Central Institute for the Deaf

Support: RR 00396
NS 03856

Our equipment is unchanged from previous reports (PR 15, E-4). In the previous year, we collected samples of different types of pathological phonation simulated by a speech pathologist. In addition to phonation in normal, soft, and loud voice modes, samples of functionally deviant voice production were collected and studied: soft-breathy voice, breathy voice, dry-hoarse voice, ventricular-hoarse voice, and harsh-hoarse voice. These samples of functionally deviant voice were compared with normal voice with regard to the appearance of the glottal waveform, the amount of perturbations of frequency and intensity, including diplophonic perturbations, and the amount of noise in the spectrum. Each of these different types of voice appear recognizably different either by the appearance of the waveform, its periodicity, or the amount of noise in the spectrum. The reflectionless tube thus appears to provide a potentially useful tool for investigating voice disorders. During the coming year, we plan to collect samples of functionally deviant phonation from a variety of subjects who exhibit such voice disorders.

E-5. Acoustic Analysis of /ra/, /la/, /ma/, /na/, /ja/, and /wa/ Spoken by Female Talkers

Personnel: R. G. Karzon, M.A., Central Institute for the Deaf
J. D. Miller, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

Six continuant sounds (viz., /ra, la, ma, na, wa, and ja/) are being analyzed with the Speech Microscope (E-2 and PR 15, E-2) to obtain the center frequencies of formants 1, 2 and 3 as a function of time. The speech microscope also provides fundamental frequency as a function of time. To date, analysis has been completed for /ra/ and /la/. In general, the formant values obtained agree with values of formants for females reported in the published literature.

The information obtained with the Speech Microscope will provide some of the guidelines for sound synthesis. The synthetic tokens of these sounds will then be used as stimuli in future experiments studying the speech-perception abilities of infants.

E-6. Spatial-Frequency Analysis of Psychoacoustically-Processed Sounds

Personnel: J. D. Miller, Ph.D., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf
N. R. Vemula, D.Sc., Central Institute for the Deaf

Support: RR 00396
NS 03856

Spatial frequency analysis is a procedure developed and implemented on the PC-1200 speech-and-hearing system in connection with our study of processing of vowel sounds by the human auditory system and the normalization of vowel sounds spoken by men, women and children. As a part of this study we have developed a spatial filter characteristic of the auditory system based upon the existing experimental data on the psychophysical tuning curves.[1] The following steps constitute the spatial frequency analysis procedure: (1) select a speech segment of two (male) or three (female) pitch periods, (2) apply a Kaiser-Bessel window to the samples of the segment to reduce the effect of end-point mismatches on the final results, (3) compute the discrete Fourier transform of the windowed samples, (4) take every second or third Fourier component from the computed transform depending upon whether a 2- or 3-pitch-period-long segment has been chosen for analysis, (5) convert the real and imaginary parts of the Fourier components into amplitudes in dB and phases in degrees, (6) convert the frequencies of the components into Mels, (7) apply Stevens ear-response-correction[2] to the dB values, (8) compute the spatial wave for the sound by sweeping the spatial filter along the Mel axis and determining the response of the filter at each position due to the components that fall under the filter characteristic, (9) apply a cosine tapering window on the spatial wave to reduce the effect of the end-point mismatches, (10) take 500 evenly spaced samples of the windowed spatial wave, (11) compute the discrete Fourier transform of the samples of the wave, (12) convert the real and imaginary components of the transform into amplitudes and phases, (13) display the amplitude and phase lines as functions of component number, (14) display the first ten components as waveforms with appropriate phases along the Mel axis, and (15) display the cumulative sums of the components as waveforms with appropriate phases along with the windowed spatial wave. Using this procedure, a study of spatial frequency components of male and female /i/, /ɪ/, /ɑ/, /æ/, /ɛ/, and /u/ sounds has been started.

1. E. F. Evans and J. P. Wilson, "Psychophysics and Physiology of Hearing: An International Symposium," Academic Press, 1977.

2. S. S. Stevens, "Perceived Level of Noise by Mark VII and Decibels (E)," Journal of the Acoustical Society of America, vol. 51, pp. 575-601, 1972.

E-7. Vowel Normalization: Differences Between Vowels Spoken by Children, Women, and Men

Personnel: J. D. Miller, Ph.D., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf
N. R. Vemula, D.Sc., Central Institute for the Deaf

Support: RR 00396
NS 03856

Peterson and Barney[1] measured certain acoustical properties of vowels spoken by 33 men, 28 women, and 15 children. They characterized each token of a vowel by its fundamental frequency, the center frequencies of the first three formants, and their relative levels. The measures were obtained from spectrographic sections taken near the presumed centers of the vowels. For each of ten vowel categories, mean values of the measurements are given for each of the three talker groups.

We have sought transformations of the frequency scale and rules of combination so as to eliminate differences between talker groups while maintaining the differences between vowel categories. Otherwise said, we seek to maximize the differences between vowel categories in relation to the talker-group differences within vowel categories.

For this purpose, we have used nine (9) vowel categories (/i, I, ɛ, æ, ʌ, ɔ, ʊ, u, and ɝ/): three talker groups (children, women, men); and the mean values of four measures of the spectrum (F0, F1, F2, F3). We have examined transformations of these variables to technical Mels (Fant, p. 48)[2] to a special Mel′ scale based on the critical ratio (Hawkins and Stevens),[3] and to position (P) along the cochlear partition (Greenwood).[4] In each case we have considered combinations as follows [(X_1, X_2), (X_2/X_1), (log X_1, log X_2), and (log X_2/X_1)]. This pattern has been extended to include similar combinations of X_1, X_2, and X_3 and, again, similar combinations of X_0, X_1, X_2, and X_3.

If no correction is made for talker groups per se, then plotting the vowels in the space log (X_2/X_1) by log (X_3/X_2) gives excellent separation between vowel categories. For example, if one uses log (F2/F1) by log

(F3/F2) then the root-mean-square distances between vowel categories is $11.2\sigma_{wc}$, while the separation between the two closest categories is $2.4\sigma_{wc}$. The σ_{wc} is, of course, the standard deviation of the within vowel differences between talker groups. Less good, but similar results are obtained for the logs of the ratios of the formants expressed as M, M′, or P. Notice that this method of viewing the vowels does not require any normalization parameters.

A similar, but slightly better clustering of the vowels is achieved if one takes the vector [log (F1/F0), log (F2/F1, log (F3/F2)] as the descriptor of the vowel. (Here one must multiply all F0's for the male group by 1.43.) In this case, root-mean-square separation between vowel categories is $10.6\sigma_{wc}$ while the minimum separation is $3.2\sigma_{wc}$.

To state the result in another way, the mean descriptions of the vowels spoken by men, women, and children are essentially identical if the male F0 is multiplied by 1.43 and each vowel is described as a point in the three dimensional space, log (F1/F0) by log (F2/F3) by log (F3/F2).

Noting that shape of the amplitude spectrum of a speech sound when plotted on log axes will be determined by the spectrum of the glottal wave, formant locations, and their bandwidths, we interpret the above findings to mean that the vowels are characterized by their spectral "shapes" when plotted on log axes. Over the usual range of absolute spectral differences between men, women, and children the absolute location of the spectrum along the log frequency axis is unimportant. (In this view, the male F0 is lower in relation to F1, than is the similar relation for women and children because their glottal spectra demand this difference if the spectral shapes of the vowels are to be maintained.)

Results of this and other studies, along with the literature taken as a whole, suggest certain directions for a theory of vowel perception. It seems to us that any theory that requires the listener to find the values of formants will have difficulty for the following reasons. (1) In many situations formants are nearly impossible to locate by simple inspection of the amplitude spectrum. (2) Often extra formants are introduced as when the nasal cavity is opened. (3) Synthesis experiments show that satisfactory vowel perceptions can be achieved with many different formant locations, formant ratios, and numbers of formants. Our results, described above, suggest that it is somehow the spectral shape, in logarithmic dimensions, that is most important for vowel recognition.

We further note, however, that natural expressions of vowels often do not have a spectral shape that is constant over the duration of the syllable. Therefore, information obtained at different moments in time must be combined so that the intended vowel can be identified. It is also true that vowel identification cannot be badly disrupted by frequency distortion in the transmission line between talker and listener.

We are planning to pursue the notion that the spectral shape of pieces of speech of 20-50 msec duration are processed by some kind of a template-matching operation. This processing results in the description of the piece in phonetically-relevant space. Points in the space are stored until there is a silence, or a sudden change in locus, or a long period of time, such as 200 msec, has elapsed. The stored points are "examined" and "averaged" in some unknown way to arrive at the intended vowel. We will attempt to develop this model so that it is relatively insensitive to the frequency response of the transmission path from talker to listener, is relatively insensitive to the exact locus of the spectral patterns in log I by log F space, and is insensitive to changes in tempo, pitch, and phonetic environment. We see no need to normalize the spectrum in relation to talker's vocal tract as the "spectral shape" in logarithmic dimensions appears to be unaffected by this.

1. G. E. Peterson and H. L. Barney, "Control Methods Used in a Study of the Vowels," Journal of the Acoustical Society of America, vol. 24, pp. 175-184, 1952.

2. G. Fant, Speech Sounds and Features, MIT Press, Cambridge, MA, 1973.

3. J. E. Hawkins, Jr. and S. S. Stevens, "The Masking of Pure Tones and of Speech by White Noise," Journal of the Acoustical Society of America, vol. 22, pp. 6-13, 1950.

4. D. D. Greenwood, "Critical Bandwidth and the Frequency Coordinates of the Basilar Membrane," Journal of the Acoustical Society of America, vol. 33, pp. 1344-1356, 1961.

E-8. Frequency Transposition of Synthetic Vowel Sounds

Personnel: J. D. Miller, Ph.D., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf
N. R. Vemula, D.Sc., Central Institute for the Deaf

Support: RR 00396
NS 03856

In an earlier pilot study one of us attempted to transpose 2-formant representations of the vowels /i, æ, a, u/ along the human cochlea by maintaining the distances between formants and their widths in millimeters. Shifts of $\pm$ 3 mm from so-called "target" values were studied. In this case, however, vowel color was not maintained as the absolute locations of the formants were shifted.

We have now synthesized complete vowel spectra in a manner which is outlined as follows. A serial synthesizer is used. Glottal waves have been developed for male and female voices which follow the spectral envelope described by Monsen and Engebretson.[1] The bandwidths of the first three formants are specified by a curve fitted to the combined data of Dunn[2] and of Fujimura and Lindqvist.[3] Separate but similar curves are derived for men and women. Finally, the geometric means of the ratios (F2/F1), and (F3/F2) are found for the mean data of men, women, and children from Peterson and Barney.[4] The ratios of F1/F0 are geometrically meaned for women and children and calculated separately for men. Higher poles and their bandwidths and the general method of synthesis are as specified in Burdick and Miller.[5]

So-called normal vowels are synthesized for a talker group by taking mean values of F1 from Peterson and Barney and then calculating or "looking-up" all other parameters (i.e., F2, F3, etc.) as described. This is done for the vowels /i, I, ɛ, æ, ʌ, ɔ, ʊ, u, ɝ/. These sets are then transposed by multiplying all synthesis parameters by the desired fraction. This method maintains the spectral shape of the vowels when plotted as log axes.

The so-called normal vowels are highly intelligible. Transposition appears to work well over the range required to explain the common vowel qualities of vowels spoken by men, women, and children. Previous research with naturally spoken syllables (Daniloff et al.)[6] is perfectly consistent with this interpretation. Of course, this evidence converges with that from our studied of vowel normalization in that the common vowel qualities of vowels spoken by men, women, and children can be explained in terms of their similar spectral shapes when plotted on log axes.

1. R. B. Monsen and A. M. Engebretson, "Study of Variations in the Male and Female Glottal Wave," Journal of the Acoustical Society of America, vol. 62, pp. 981-993, 1977.

2. H. K. Dunn, "Methods of Measuring Vowel Formant Bandwidths," Journal of the Acoustical Society of America, vol. 33, pp. 1737-1746, 1961.

3. O. Fujimura and J. Lindqvist, "Sweep-tone Measurements of Vocal-tract Characteristics," Journal of the Acoustical Society of America, vol. 49, pp. 541-558, 1971.

4. G. E. Peterson and H. L. Barney, "Control Methods Used in a Study of Vowels," Journal of the Acoustical Society of America, vol. 24, pp. 175-184, 1952.

5. C. K. Burdick and J. D. Miller, "Speech Perception by the Chinchilla: Discrimination of Sustained /a/ and /i/," Journal of the Acoustical Society of America, vol. 58, pp. 415-427, 1975.

6. R. G. Daniloff, T. H. Shriner, and W. R. Zemlin, "Intelligibility of Vowels Altered in Duration and Frequency," Journal of the Acoustical Society of America, vol. 44, pp. 700-707, 1968.

E-9. Computer-Controlled Testing of a Hearing-Impaired Person's Ability to Identify the Sounds of English

Personnel: J. D. Miller, Ph.D., Central Institute for the Deaf
G. Friedman, M.S., Central Institute for the Deaf
M. Skinner, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

A hearing-impaired client was tested with the MEGS[1] system, which has been described in earlier reports (PR 11, G-7; PR 12, G-7). The patient listened to speech sounds delivered by the MEGS system to a special hearing aid developed at CID. The aid allows frequency selective control of both gain and maximum outputs. This was accomplished by dividing the spectrum from 266-6000 Hz into 9 channels with independent control of gain and limiting in each channel. The gains were adjusted to bring the average level of speech in each channel to the listener's most-comfortable-listening level and maximum outputs were adjusted to just match the listener's threshold of discomfort. The aid was further manipulated so that three passbands could be obtained. These were: (1) 266-6000 Hz; (2) 353-4242 Hz; and (3) 530-2121 Hz.

Three tests of the MEGS system were used. "Incon" includes all 53 possible beginnings of English words combined with the vowel /a/. "Fincon" includes all of the 55 single morpheme endings of monosyllabic words that can occur in English. Again these are combined with vowel /a/. "Vownu" includes the twenty syllabic nuclei that can occur in English. These are spoken in an /hVd/ context. The speech of one female talker is used.

The MEGS system begins the test by drawing from an entire list randomly. Sounds that are correctly identified are assigned to an "out" list from which items are chosen less frequently. Sounds that are incorrectly identified or used incorrectly as responses remain in or are transferred to the "in" list. Items on the "in" list are presented more frequently. In this way the testing quickly converges on those items that are most troublesome for the listener.

The subject learned the task quickly and was given about 30 minutes of practice with each test prior to final testing. Final testing includes

a 150-trial test on each test for each bandwidth. Bandwidth effects were revealed in overall percent correct-identifications, the average size of the "out" list in percent, and in the rate of growth of the "out" list. Error analysis pinpoints those sounds that are most difficult for the listener. For example, the percent of correct identifications from wide to narrow bandwidths were 37, 22, and 15% for Incon; 20, 17, and 10% for Fincon; and 39, 37, and 19% for Vownuc. The most difficult items were consonant cluster involving /r/ and /l/ such as /gra/, /ra/ and /fa/ for Incon; final voiceless fricatives and stops and their blends with /l/ and /n/ for Fincon, and the r-colored vowels for Vownuc. These results and discussion with the subject, herself, suggest that this method will be extremely useful for clinical research, but would need considerable simplification to be useful in routine clinical work.

1. J. D. Miller, A. M. Engebretson, S. A. Garfield, and B. L. Scott, "New Approach to Speech Perception Testing," Journal of the Acoustical Society of America, vol. 57, supplement, p. 548, April, 1975.

E-10. Implementation of the Stevens & House Articulatory Model for Speech Synthesis

Personnel: N. R. Vemula, D.Sc., Central Institute for the Deaf
A. M. Engebretson, BCL and Central Institute for the Deaf
J. D. Miller, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

In order to analyze and evaluate the acoustic performance of the vocal tract during vowel phonation, Stevens and House[1] have considered the tract as a nonuniform, cylindrical tube excited at the glottal end and terminated in an appropriate radiance impedance at the lip-end. Our goal in the implementation of the model is to study the effect of systematic changes in the articulatory parameters on the first and the second formant frequencies in connection with the study of vowel normalization described in E-4. The tube has three parts: (1) the glottal part which is assumed to be fixed and consist of two pieces: the first piece with a parabolic radius function from the glottis up to 3 cm along the tract and the second piece with a constant radius of 3 cm to the middle part, (2) the middle part corresponding to the tongue constriction with parabolically increasing radius on either side of the constriction, and (3) the cylindrical lip piece. For a fixed length of the lip piece the model has three parameters: (1) the location of the tongue constriction from the glottis, (2) the radius of the constriction, and (3) the lip area/length ratio.

The lip area/length ratio is taken as a parameter rather than the area because it is the area/length ratio or conversely the length/area ratio that determines the mass reactance at the lips. In our implementation of the model the lips are assumed to be terminated with an infinitely long terminator tube. The first and second formant frequencies are determined as follows. The tube is discretized into 0.5 cm long sections and each section is represented by a uniform cylinder with a cross-sectional area such that the cylinder has the same mass reactance as the original nonuniform section. The all-pole transfer function of the tube is then determined from the reflection coefficients at each section. The formant frequencies are computed from the roots of the transfer function and then converted into Mels. The results indicate that logarithmic decrements in the lip area/length ratio combined with corresponding change in the distance of the constriction from the glottis yield approximately straight lines in the Mel M1-M2 plot that correspond to certain vowel categories.

1. K. N. Stevens and A. S. House, "Development of a Quantitative Description of Vowel Articulation," Journal of the Acoustical Society of America, vol. 27, pp. 484-493, 1955.

E-11. General Software Development

Personnel: N. R. Vemula, D.Sc., Central Institute for the Deaf

Support: RR 00396
NS 03856

A number of FORTRAN routines have been written and added to the speech and hearing system software library. They can be classified as (1) scope display routines, (2) mathematical routines, and (3) miscellaneous routines. The previous scope display routines enable us to look at the spectral information corresponding to a speech segment in the following ways: (1) spectral lines with amplitudes expressed in dB corresponding to the different harmonic components displayed on linear frequency scale, (2) spectral lines on logarithmic frequency scale, and (3) phase lines in degrees on linear frequency scale. The present scope display routines show the spectral information in a variety of ways: (1) spectral lines on Mel[1] scale, (2) spectral lines on logarithmic Mel scale, (3) energy levels in dB in different 1/3-octave filter bands covering the frequency range 0 Hz - 10 kHz on logarithmic frequency scale, where the center frequencies and bandwidths of the filters correspond to those of the Bruel and Kjaer audio frequency spectrometer, (4) specified number of first several spectral lines displayed with their harmonic numbers shown

at the bottom, (5) specified number of first few harmonic components displayed as sine waves with appropriate phase as functions of time, (6) cumulative sums of first few components and the original speech segment as functions of time. Another display routine takes x and y coordinates for specified number of points and displays them on the scope with specified scales for the axes.

A number of routines written in connection with the psychoacoustics of speech sounds are among the mathematical routines. The Mel routine gives the Mel value for a given frequency, whereas the "MELTOHZ" routine does the reverse operation. GREENWOODMAP and AMEMAP are subroutines that calculate mapping functions of distance along the cochlea as a function of frequency. The first subroutine implements a Greenwood[2] mapping function. The second routine implements a modified Mel function that yields a closer fit to critical bands at low frequencies. EARCORCTN computes the Stevens ear-response correction[3] in dB for a given frequency to determine the perceived sound level from the actual one. "HSCRBAND" computes the critical band in Hz for a specified frequency using a 7th degree polynomial fit to Hawkins and Stevens critical band data[4] at different frequencies. A number of routines have been written to compute the spatial wave along the cochlea corresponding to a specified speech segment.

The cluster analysis routine takes points corresponding to different categories for different experiments or groups and gives the variance between categories, variance within categories, and also minimum sphere-to-sphere distance and minimum center-to-center distance for spheres representing the categories. Each point can have up to four coordinates.

Among the miscellaneous routines are the improved versions of waveform zero-crossing routines, which perform a linear interpolation between samples to determine the zero-crossing time. These routines give a very accurate measurement of the fundamental frequency of the waveform.

1. G. Fant, Speech Sounds and Features, MIT Press, Cambridge, MA, 1973.

2. D. D. Greenwood, "Critical Bandwidth and the Frequency Coordinates of the Basilar Membrane," Journal of the Acoustical Society of America, vol. 33, pp. 1344-1356, 1961.

3. S. S. Stevens, "Perceived Level of Noise by Mark VII and Decibels (E)," Journal of the Acoustical Society of America, vol. 51, pp. 575-601, 1972.

4. J. E. Hawkins, Jr. and S. S. Stevens, "The Mashing of Pure Tones and of Speech by White Noise," Journal of the Acoustical Society of America, vol. 22, pp. 6-13, 1950.

F. Central Nervous System Diseases and Electroencephalogram Analysis

The Biomedical Computer Laboratory's involvement in clinical neurology, neurosurgery, and in neurophysiological research reaches back to the Laboratory's beginnings. In 1965 and 1966 a LINC computer at BCL was applied in processing radioisotope brain-scan data transmitted over telephone lines from the hospital radiology unit, and in 1966 a LINC-controlled evoked-response display system was installed, providing neurosurgeons in the operating room with continuous EEG monitoring capability via closed-circuit television. In 1969 and 1970 a LINC computer was interfaced to a six-probe system designed by the radiology department for in-vivo cerebral blood-flow and oxygen-metabolism studies employing cyclotron-produced radioisotopes. The next two years saw further development of this approach with the construction of a twenty-six-probe brain blood-flow and metabolism unit capable of increased spatial resolution.

At this juncture it was recognized at BCL that new initiatives in central nervous system and other radiotracer studies must stem, in part, from an improved understanding of the manner in which the underlying physiological phenomena reveal themselves through gamma rays and annihilation photons to the external data-gathering instruments. Thus, in collaboration with scientists at Washington University and at other institutions, the Laboratory undertook a substantial augmentation of its program in tracer kinetics by expanding its activities in physiological modeling and parameter estimation. These collaborative efforts led to successful quantitative methods of studying in-vivo such diverse processes as brain-glucose transport and metabolism, blood-brain-barrier permeation of water, alcohols, ammonia, and carbon dioxide, and the autoregulation of cerebral blood volume and blood flow.

Research efforts at BCL in application of computers and mathematical models to CNS disease management and EEG analysis, reported last year in PR 15, have continued to be productive: advances have been made in all the projects previously described. A system to simplify the collection and processing of averaged visually evoked potentials has been developed and successfully tested. Progress has continued in the development of computerized systems for automatic processing and monitoring of signals generated in the neurophysiology laboratory and during neurosurgical procedures. The computerized autoradiographic-image-processing system for neuroanatomy begun last year is now nearing completion. Our long-standing collaboration with scientists at Washington University and at other institutions in studies of CNS function using cyclotron-produced radiopharmaceuticals has continued to be fruitful. Progress in this and in our other involvements in CNS research during the past year is reported in the following.

F-1. Visual Evoked Response

Personnel: G. J. Blaine, BCL
M. W. Browder, BCL
L. A. Coben, M.D., Neurology
J. K. Montrose, BCL
S. R. Phillips, BCL
H. W. Shipton, BCL and Electrical Engineering
L. J. Thomas, Jr., BCL

Support: RR 00396
MH 31054

The visual evoked response (VER) or potential (VEP) is used as an indicator of cerebral physiology. Electrophysiological responses evoked by repeated visual stimuli are separated from other ongoing electrical activity by a signal-averaging process. Features extracted from the averaged responses to stationary white-flash and to reversing black-and-white checkerboard patterns are to be included with behavioral measures and cerebral structure metrics in a temporal study of patients with senile dementia.

A system to simplify the collection and processing of averaged visual evoked potentials (AVEPs) has been developed. The overall system can be described as a "loosely coupled" distributed processing system. The coupling between components of the system is in the form of data transfer via machine-readable magnetic storage media, i.e., flexible diskette and industry-compatible nine-track magnetic tape.

A microprocessor-based system was developed to provide flexible parameterization of clinical protocols and to permit collection of AVEPs.[1] The salient features are summarized in Table 1. Feature-detection algorithms were developed on a minicomputer system to simplify and improve the accuracy of previously used manual scoring methods. An editing system was also developed to allow operator verification and editing of the features located by the automatic system.[2] The parameters of interest are then included in a statistical database for further analysis on a large computer.

In order to evaluate the performance of the automatic feature-extraction (AFE) system, data concerning the operator editing of AVEPs is captured. These data are used to monitor the amount and type of editing being performed and will aid in the further tuning of the AFE algorithm, if necessary.

AVEP data from 50 subjects have been analyzed. As expected, peak P2 is the most consistent and has required the least amount of editing. Due to the contextual nature of the other peaks, a larger number of them required editing. The amount of editing necessary for each peak is summarized in Table 2.

Table 1

Acquisition-System Parameters

Sampling Rates:

EEG	64 Hz
Averaging	500 Hz

Stimulus Rates: 0.25 to 3.60 Hz
Number of Epochs Averaged: 1 to 256
Epoch Length: 200 to 1000 ms
Resting EEG Duration: 0 to 64 sec
Pre-Stimulus Delay: 8 to 184 ms
Rejection Levels: 0 to 100% of full scale
Triggers: Internal or External
Stimuli: Randomized or Periodic

Table 2

AFE Performance Study
(data from 50 subjects, 400 AVEPs)

Peak	Percent Modified
N1	34
P2	7
N2	12
P3	23
N3	35

1. J. K. Montrose, "Acquisition and Processing of the Visual Evoked Response," Master of Science thesis, Sever Institute, Washington University, St. Louis, Missouri, December 1979; also BCL Monograph No. 373.

2. M. W. Browder, G. J. Blaine, J. K. Montrose, L. A. Coben, and L. J. Thomas, Jr., "Visual Evoked Potential: Computer-Assisted Acquisition and Processing," Proceedings of the Fourth Annual Symposium on Computer Applications in Medical Care, Washington DC, November 1980, in press.

F-2. Development of an Automated System for the Monitoring of Epileptic Patients with Indwelling Electrodes

Personnel: C. F. Pieper, M.S., Neurological Surgery
S. A. Golden, B.S., Neurological Surgery
S. Goldring, M.D., Neurological Surgery

Support: NS 14834
Washington University

The crosspoint matrix (PR 15, F-2) has been expanded to allow monitoring of arrays with 52 electrodes. The full matrix has been used with eight patients and has performed well. Grounding the matrix outputs as they enter the low-level EEG amplifiers was found to adequately quiet the pen writers during electrical stimulation of the brain. A prototype of the previously proposed EEG amplifier (PR 15, F-3) has been satisfactorily tested, and a bank of such amplifiers has been constructed. Software for their control is under development.

A MINC [Digital Equipment Corporation (DEC)] system has been delivered and plans are being formulated for a sixteen-channel peristimulus averaging system. Accordingly, a sixteen-channel A/D converter has been constructed for use with our EEG amplifiers and the MINC. This portion of the system will make possible the collection of the averaged sensory evoked response (SER) to median-nerve stimulation.

Plans are also being developed for a digital communication system to permit recording the SER from the operating room and various patient areas without transporting the MINC. The communication system will have sufficient capacity to permit simultaneous monitoring of seizure activity and for collection of the SER. The monitoring system will be based on a PDP 11/34 (DEC) and will permit retention and display of sixteen channels of EEG from up to five seizure episodes.

F-3. In-Vivo Measurements of Regional Blood Flow and Metabolism in Brain

Personnel: M. E. Raichle, M.D., Neurology and Radiology
R. L. Grubb, Jr., M.D., Neurological Surgery
C. S. Higgins, A.B., Radiology
S. Lang, Ph.D., Physiology and Biophysics
K. B. Larson, BCL
J. Markham, BCL
N. A. Mullani, BCL
M. M. Ter-Pogossian, Ph.D., Radiology
T. J. Tewson, Ph.D., Radiology
M. J. Welch, Ph.D., Radiology

Support RR 00396
HL 13851
NS 06833
Washington University

We have continued our previously reported efforts in the study of central-nervous-system hemodynamics and metabolism. Our immediate objective has been the development of techniques employing biochemically significant compounds labeled with cyclotron-produced isotopes (PR 15, F-3), suitable external-radiation-detection systems (PR 15, B-5; B-9), and appropriate mathematical models (PR 15, F-3) for the in-vivo and regional study of basic biological processes and pathology within brain. Our ultimate goal is to use these techniques to provide the quantitative physiological and biochemical measurements in humans necessary to understand central-nervous-system disease, as well as to formulate specific therapies and monitor their results.

Our previously reported studies of ammonia transport and metabolism in brain (PR 15, F-3) have led to a new distributed-parameter regional model of the cerebral circulation that takes into account the effects on tracer transport of capillary heterogeneity within an external-detector spatial-resolution element. This model permits, apparently for the first time, interpretation of externally acquired radiotracer count-rate data in terms of regional-average or voxel-average parameters describing hemodynamics and tracer transport, thus avoiding previous inconsistencies arising from the application of single-capillary models to heterogeneous structures.

F-4. Studies of an Image-Processing System for Neuroanatomy

Personnel: A. J. Gray, BCL
G. J. Blaine, BCL
J. G. Dunham, BCL and Electrical Engineering
V. W. Gerth, Jr., BCL
E. G. Jones, M.D., Ph.D., Anatomy
J. S. Massey, BCL
J. L. Price, Ph.D., Anatomy
L. J. Thomas, Jr., BCL
T. A. Woolsey, M.D., Anatomy

Support: RR 00396
NS 15070

Morphological studies of the organization of the central nervous system utilize radiolabeled precursor substances to visualize nerve-cell connectivity. Radiolabeled substances injected into or around nerve-cell bodies are incorporated into macromolecules and are transported down the axons to accumulate in their terminals. The spatial distributions of the radiolabels are then revealed using autoradiography, a technique in which photographic emulsions are exposed in close contact with tissue sections. The resulting images, consisting of silver grains formed in the emulsion by action of the ionizing radiation, represent the radiolabel distributions in the tissue sections. Since the silver grains are relatively uniform in size and confined to the plane of a photographic emulsion, the images are particularly amenable to quantification using a combination of bright-field and dark-field microscopy. For quantification of the autoradiographs, a second-generation microscopy-based instrument is being implemented. The instrument, which has been previously described (PR 15, F-4), will provide a computer-assisted means for silver-grain counting and specimen review.

The instrument consists of an automatic stage-control processor (ASCP) that positions the microscope stage, a video processor and image analyzer (VPIA) that accepts video data from the imaging device and extracts grain-count densities and other image parameters, an operator control panel (OCP) from which the user can interact with the system in an efficient manner, and a supervisory processor that coordinates the network. All of these elements are interconnected by the IEEE-488 instrumentation bus, a key feature of the design. The IEEE-488 bus provides a standardized interface protocol, guarantees that the various modules can function independently, and allows for easy modification and expansion. Currently, the ASCP has been completed. Both the hardware and software for its Motorola-6802 microprocessor have been built, tested, and documented. Modifications and additions to the Zeiss universal microscope are likewise complete, with a motorized focus control and XY overtravel limit switches being the major items. A charge-injection device (CID) television camera has been mounted and optically coupled to the microscope.

The supervisory processor, consisting of an LSI 11/2 processor with a 64-kbyte MOS memory, a dual double-density floppy diskette, a "smart" CRT terminal, and a printer, has been configured and is in routine use. The supervisory processor also includes an IEEE-488 I/O card and software driver for its RT-11 operating system. A library of FORTRAN-callable subroutines supports communication over the IEEE-488 bus with the ASCP, OCP, and video processor. Initial tests of communication between the ASCP and supervisory processor have been quite successful, and work has begun on the software design of the grain-counter system executive. Emphasis is on a modular and highly structured design due to the potentially large size of the program and the desire to accommodate modifications easily.

The OCP circuitry has been designed, and most of the wirewrapping has been accomplished. The layout of the control panel has been established, the enclosure fabricated, and most of the hardware (alphanumeric display, push buttons, joystick, etc.) has been mounted. Final assembly work, panel wiring and hardware verification are in progress. Software generation for the OCP will be under way shortly.

A General Electric television camera with a 242-by-236 picture element (pixel) CID imager is used for image acquisition. The CID has very low lag, virtually no shading, and no burn problems compared to conventional tube imagers. Compared with charge-coupled devices, CID imagers are reported to have better sensitivity, lower dark current, and lower crosstalk between pixels. This particular camera also has built-in outputs for digital video and timing signals, which simplify interfacing the camera to digital equipment. A detailed analysis and verification of the digital interface has been completed, and a slow-scan interface to a PDP-11/34 has been built and tested, allowing images to be loaded into the minicomputer for evaluation. Preliminary analysis of the video data has also been completed. Several discrepancies between camera documentation and test results were discovered and reported to General Electric.

The video processor's structure has been designed; it features extensive use of off-the-shelf equipment, which is expected to enhance its exportability and reliability. Image storage (8 bits/pixel), analysis, and display will be performed primarily by one device - a Lexidata 3400 image-processing system. This commercially available unit contains a 256-by-256-by-10-bit image memory, circuitry for generating a raster-scan display of the image on a color CRT along with color graphics and text, and a high-speed 12-bit programmable processor. The Lexidata unit is controlled by an LSI 11/23 processor with a 64-kbyte memory. The LSI 11/23 communicates with the supervisory processor via the IEEE-488 bus, interprets commands from the supervisor, and configures the Lexidata unit to perform the desired operations, either by invoking PROM-based utility routines, or by downloading special-application microcode to the Lexidata unit's writable control store. Image acquisition from the CID camera, contrast enhancement, thresholding operations, filtering and grain counting are examples of typical video processor tasks. A library of FORTRAN callable subroutines facilitates use of the image processor.

The design of the switching hardware between the LSI 11/23, the camera, and the Lexidata unit is only just beginning due to the delays in verification of the camera's interface timing by General Electric. The goal is to design this high-speed switch with flexibility sufficient to permit the addition of a disk storage device for archiving images in digital form.

Initial studies of image-processing algorithms are well under way, although considerable work remains. Present plans call for first-generation grain-count algorithms that are modest improvements on those used in the first-generation grain counter.[1]

1. D. F. Wann, J. L. Price, W. M. Cowan, and M. A. Agulnek, "An Automated System for Counting Silver Grains in Autoradiographs," Brain Research, vol. 81, pp. 31-58, 1974.

F-5. A Correlation Technique for the Study of Visually Evoked Potentials

Personnel: H. W. Shipton, BCL and Electrical Engineering

Support: RR 00396
Washington University

Using the visual-stimulus generator previously described (PR 15, F-5), a small number of recordings has been made in a volunteer population (N = 4) with equivocal results. There is reason to think that the method will provide information regarding the topology of the visual cortex. The present stimulator, while adequate for initial studies, will be modified to provide a larger stimulus area.

For administrative reasons, work on this project will be suspended until Spring 1981.

G. Supporting Activities

Activities at BCL which contribute to the goals of more than one major program of the laboratory or to the needs of individual users who can benefit from the special expertise of the staff and the inventory of computer and test equipment are called supporting activities. Service to users does not follow the usual computation-center pattern. No fee schedule has been established, nor is there a centralized facility. Instead, senior laboratory staff members consider requests from investigators for assistance in addressing biomedical computing problems. Investigators may be directed to commercial vendors or existing fee-for-service facilities. Other researchers may be advised of the unavailability of appropriate technology. The remaining investigators may have problems that match the special capabilities within BCL. Usually, such a project is assigned to a staff member with similar experience. If the project can be completed quickly, the investigator has his or her results and a short note describing the work will appear in the annual report and in the open literature if appropriate. Other projects occasionally prove impractical and the best alternative is recommended. A few of the user projects may develop into major initiatives within the laboratory. Most of the major projects began in this fashion and we value the opportunities that supporting activities provide.

Although the projects reported in this section span a variety of topics, they can be grouped conveniently as biomedical applications, system development aids, and digital hardware designs. The biomedical applications represent new initiatives in which basic exploration is being conducted, which may or may not ultimately result in a major, long term program. Two examples are the continued collaboration with the Department of Biochemistry relating to the development of microcomputer systems for laboratory automation and a new collaboration with the Department of Genetics studying the restriction map of DNA sequences. The previously reported radiation treatment planning project has matured to the extent that is now reported under Quantitative Imaging (B-14, 15, 16). Even in cases where an extended effort does not materialize, the relationships which are cultivated frequently prove beneficial to future work.

System development aids mostly benefit the BCL staff, but also are utilized by other groups where appropriate. An excellent example here is the microprocessor development support system which, although still evolving, is an almost routine tool used in data acquisition, signal processing, and control applications. System software development for the PC-1200 and the AUGAT wirelist program reported here are also widely used in supporting a variety of projects.

The digital hardware designs reported in this section are frequently one-time, special purpose designs. The design of the ECG cassette recorder is an example of such a project. In contrast, other designs may have wide appeal and construction of multiple copies can easily be envisioned. The USD (Universal Storage Device) is such a design and is widely applied by users with a need for off-line data acquisition and local mass storage.

G-1. Microprocessor Development Support

Personnel: M. W. Browder, BCL
R. J. Arnzen, BCL
R. M. Arthur, BCL
G. J. Blaine, BCL
W. D. Gillette, Ph.D., Computer Science
D. W. Goldfarb, Computer Science
R. K. Hartz, BCL
S. A. Phillips, BCL

Support: RR 00396
Washington University

Our microprocessor development support includes a FORTRAN-based cross-assembler, FOCRAS, intelligent console (InC) and a small library of "standard" M6800 system modules. At present FOCRAS provides cross-assembler support for the 6800, 8080, and 6502 instruction sets and is currently operational on Texas Instruments Model 980B, Artronix Modulex, and Digital Equipment Corporation Model PDP-11 minicomputers. A collection of generally useful subroutines into a shared microprocessor library which is accessed by the FOCRAS linking loader has been established. The Intelligent Console is itself a microprocessor-based instrument which is used to assist both hardware and software development of microprocessor-based systems.

New target-dependent hardware and software were implemented to upgrade the InC to provide support for development of systems utilizing the M6802 microprocessor. The InC now supports development of systems based on the M6800, M6802, and Intel 8080 microprocessors.

Investigation into the architectures of 16-bit microprocessors such as the M68000 and the Intel 8086 showed that a considerable redesign effort would be required to extend the InC to support these processors. Based on this finding and the commercial availability of satisfactory support products, it was decided to not expand the InC to support 16-bit microprocessors at this time.

The design phase of a cross-assembler for the M68000 based on FOCRAS has been completed. Implementation of the cross-assembler will proceed during the coming year.

A software floating point package for use with the M6800 has been obtained. The package is written in position independent code and is available in a 1K 2758 EPROM or as a load module compatible with FOCRAS.

G-2. System Software Development for the PC-1200

Personnel: D. W. Stein, Jr., BCL
G. H. Brandenburger, BCL

Support: RR 00396

Software development for the PC-1200 was limited to making user-requested additions and changes to the existing BDOS operating system (PR 15, G-2). This policy reflects a commitment to provide a level of support for the system equivalent to the system's level of use.

The software development is divided into two categories: commands and subroutines.

I. Commands

1) The magnetic tape read command has been updated to provide optional EBCDIC to ASCII character translation and a logical record length parameter.

2) The magnetic tape write command has been updated to provide optional user specified blocking of logical records.

3) A "command generator" command has been added to enable easier construction of run files from an index.

II. Subroutines

The following subroutines have been added to the BDOS library.

1) A subroutine to perform binary-coded decimal subtraction.

2) A subroutine to perform EBCDIC to ASCII character translation.

3) A subroutine to perform general purpose reads and writes to the universal storage device (G-3).

4) A package of seven subroutines to perform standard FORTRAN sequential file input/output functions for LINC tape and BCL disc files. Highlights to this package are:

   a) rewind, backspace, and end-of-file handling capabilities;
   b) multiple files may be in use concurrently; and
   c) input/output is invoked with standard READ and WRITE instructions.

All existing documentation files have been updated to reflect the changes and new documentation files have been written for the new software.

The updated versions and new software are contained on a separate LINC tape so that only the users desiring the updates need modify their existing BDOS system.

G-3. A Universal Storage Device

Personnel: R. W. Hagen, BCL
R. J. Arnzen, BCL
G. H. Brandenburger, BCL
M. W. Browder, BCL
B. R. Hieb, M.D., Jewish Hospital
R. E. Olson, A.A.S., Computer Systems Laboratory
S. R. Phillips, BCL

Support: RR 00396

The Universal Storage Device (USD) is a convenient, portable instrument for acquiring, storing and transferring the data associated with a variety of research activities. The acquisition of analog signals is achieved through the USD's four analog input channels. Analog voltage signals are digitized to twelve bits of precision and stored on flexible diskette media. Signal sampling rates of up to two thousand (2000) samples per second are available. Digital information can be stored on and/or retrieved from a diskette through the instrument's RS-232 serial communication interface. Eight USDs have been constructed and several research activities have benefitted from the use of the instrument.

During the past three months a USD has been in operation at the Jewish Hospital, Department of Psychology where it is used to load data into a psychiatric interview system developed by the Computer Systems Laboratory of Washington University. This system is used daily and has worked reliably since its installation. Another USD is kept at the Computer Systems Laboratory to support ongoing programs including the constant area tonography system (C-2) and psychiatric interview system. The constant area tonography system has been in use for over a year in the Department of Ophthalmology where a USD serves as a bootstrap loader for a minicomputer system as well as a means for collecting the analog data developed during the course of the constant area tonographic studies.

The USD has also been used to transfer digital data between the Laboratory of Ultrasonics at the Department of Physics and BCL. Ultrasonic measurements such as tomographic projections and C-scan images, acquired by a HP 9825 calculator system, are transferred to the USD using the RS-232 serial link. These data are later transferred from the USD to a PC-12 where they are processed and displayed using CUTARSYS (B-1) software package, on video monitors with Digivision (G-5) or on paper using a Versatec electrostatic plotter.

G-4. A Low-Cost ECG Cassette Recorder

Personnel: H. D. Ambos, BCL and Medicine (Cardiology)
T. L. Weadon, BCL

Support: RR 00396
HL 17646

An eight bed Hewlett-Packard computerized telemetry system has been installed in the Barnes Hospital Coronary Care Unit step-down facility. Since it is crucial for the computer system to accurately detect ventricular tachycardia, ventricular fibrillation, asystole, and supraventricular tachycardia, a device was needed which could easily perform daily tests on the entire system. To accomplish this, a standard audio cassette recorder was modified to record and play back five minute segments of ECGs ending in these critical arrhythmias. A separate ten minute segment of supraventricular tachycardia, ventricular tachycardia, and asystole was also recorded.

A voltage-controlled oscillator transforms the ECG waveform into a 1.11 kHz frequency-modulated sine wave which is then recorded on tape. A phase-locked loop is used to demodulate the playback signal and a 30 Hz low pass filter conditions and attenuates the signal. The output to the bedside telemetry transmitter is a two to five millivolt ECG signal. The test system parts cost was about ninety dollars, including the cost of the cassette recorder.

G-5. A General-Purpose Digital Display System: Digivision

Personnel: G. H. Brandenburger, BCL
R. M. Arthur, BCL
D. W. Stein, Jr., BCL
J. R. Thompson, BCL
T. L. Weadon, BCL

Support: RR 00396

Digivision (PR 15, G-9) was augmented with an additional two bit-planes to bring the total grey-scale resolution to 6-bits. Grey-scaled images now exhibit considerably less contouring artifact due to undersampling of the grey-scale range.

Software and hardware upgrading has accomplished the following: a) the TI-980 computer associated with the adaptive beamforming for quantitative ultrasonic imaging (B-5) can now access digivision. Tests using previously recorded M-mode images have demonstrated the value of the 6-bit grey-scale resolution. The 512 by 480 spatial resolution also appears adequate for this work; b) diagnostic routines were enhanced to facilitate hardware debugging.

G-6. A System for Multiplexed Cinemicrography of Cultured Cells

Personnel: R. J. Arnzen, BCL
V. W. Gerth, Jr., BCL
R. R. Heye, M.S., Radiology
L. J. Tolmach, Ph.D., Anatomy and Radiology

Support: RR 00396
CA 04483

In recent months the hardware and software development for a system that will permit multiplexed time-lapsed cinemicrography of cultured cancer cells (PR 15, G-10) has been completed and is currently being evaluated in a 'warm room' where it will ultimately be used for its intended research work. Installation has proceeded to the point where trial exposures have been made and evaluated.

Among the objectives completed over the past year were the following:

1) Completion of the unique cine camera for multiplexed cinemicrography.

2) Adaptation of a motorized stage and focus control to a microscope.

3) Construction of a pedestal for optically and mechanically coupling the microscope and camera.

4) Completion and initial testing of software to control the system.

5) Installation and initial testing of the system in its final environment.

Initial evaluations of the system have suggested some modifications to software and hardware. Software changes are being made to avoid resonance points in the camera stepping-motor drive while a dish holder used as an environmental chamber for the cultured cells on the microscope stage is being modified to eliminate a problem of condensation of water vapor on the lid which interferes with contrast optics. This work is currently under way, and full scale experiments with the micrography system will begin within the month.

G-7. Microcomputer Systems for Biochemistry Laboratory Automation

Personnel: M. C. Jost, BCL
W. F. Holmes, BCL

Support: RR 00396

This project has been concerned with the development of a flexible set of hardware and software modules for use in automation of control, data collection, and data processing for certain analytical instruments used routinely in biochemical research, such as amino acid analyzers, gas chromatographs, spectrophotometers, and ultracentrifuges. These applications typically require on-line data acquisition and control with modest speed requirements. Most applications require relatively simple on-line data reduction, although some require more sophisticated post-run calculations. Costs must generally be kept to a few thousand dollars, even less for the simpler instruments.

Previous reports (PR 12, F-1; PR 13, F-1; PR 14, G-12 and G-19; and PR 15, G-13) have described the selection of components for a stand-alone LSI-11-based microcomputer system and the development of hardware and software modules for analog input, keyboard entry, and printer and plotter output. Development of additional data acquisition and graphic display software modules suitable for use in the initial application and automation of a high speed, sensitive amino acid analyzer developed in the Department of Biochemistry also was reported.

These previous reports discussed the combination of all system components with a dual floppy disk system to form a development system housed in a 24-1/2" × 25-1/2" × 36-1/2" mobile cart. This cart is easily moved to the site of the laboratory instrument and is of a size and shape which permits on-site system development, maintenance, and improvement without excessive interference with routine laboratory and instrument operation. It was anticipated that once an application was complete, hardware for that application would be housed in a box with a control and monitoring panel on the front and connectors in the rear for analog and digital I/O and whatever peripheral devices are required, e.g. keyboard, alphanumeric printer, and/or plotter. This dedicated system would be left at the instrument site.

In the past year, however, the Department of Biochemistry has installed a Digital Equipment Corporation VAX 11/780 computer to serve as a departmental resource. This development has caused us to re-examine the goals and direction of this project in view of the altered needs of departmental investigators, technological advances, and experience gained since this project began.

The VAX functions as a large multi-user system with adjustable access priorities. Adequate memory, disk, and tape storage is available to serve the needs of the many departmental users. Printer and high speed

plotter output are available. The VAX is not configured for high speed real-time data acquisition or control. On-line instruments must therefore have a data buffer with preprocessing and control capabilities. All users are connected to the VAX via serial (RS-232) links.

The most obvious and immediate effect of the availability of the VAX in the area of laboratory instrument automation is that, in the majority of cases, it eliminates the need for a stand-alone dedicated mini- or microcomputer-based controller and data acquisition system such as we have been developing. What is needed is a type of intelligent terminal which communicates with the VAX and which relies on the VAX, to a greater or lesser extent, depending on the needs and resources of the individual investigator and the instrument being automated.

A VAX satellite terminal for use in biochemistry research laboratories to connect laboratory instruments to the VAX computer should have, depending upon the circumstances, some or all of the following features:

1) Eight or sixteen bit CPU
2) At least 4 Kbytes of RAM memory
3) Some type of permanent program storage, either PROM memory, minifloppy disk, floppy disk, or cassette recorder
4) Serial (RS-232) link to the VAX
5) Analog input and output, with the sensitivity in certain applications as low as 50-100 mV
6) User-accessible clock
7) Keyboard and CRT or LED-type alphanumeric display for communication with the user
8) Local graphic display or plotter capability
9) Local program development capability
10) Support for at least one higher level language
11) Small compact mechanical configuration
12) Adequate power

In a minimal system in which the microcomputer is used only as a dedicated controller or preprocessor and where no further system development or additional use of the system is anticipated, having only PROM memory for permanent program storage would be sufficient. Local graphic display or plotter capability, local program development capability, or higher level language support would not be necessary. Ease and extent of system use, as well as user interest, user acceptance, and user development of new applications for the system would be greatly enhanced by inclusion of these additional features, however.

We have examined in detail possible VAX satellite terminal configurations based on the Rockwell AIM-65 single board microcomputer, the Digital Equipment Corporation LSI-11 microcomputer, the Apple Computer, and the Hewlett Packard HP-85 personal computer. In each case it is possible to configure a terminal having the necessary performance and capability. The cost and ease of use for a biochemist vary considerably, however. Cost of a VAX satellite terminal would be approximately $2000 with the AIM-65, $2000 - $4000 with

the Apple Computer, $4500 - $5500 with the Hewlett Packard HP-85, and $4000 - $9000 with the LSI-11 microcomputer. The Apple Computer or HP-85-based satellite terminal would be easiest for a biochemist to use.

Again, which of these alternatives is selected will depend on the needs and both the financial and technical resources of the individual investigator. Furthermore, it must be concluded that the LSI-11-based microcomputer system which we have been using, developed along the guidelines outlined above for VAX satellite terminals, represents but one of a spectrum of equally attractive solutions to the problem of automating instruments present in biochemistry laboratories.

G-8. A Wiring-List System for Augat and TM-500 Hardware

Personnel: M. W. Browder, BCL
C. A. Branyan, BCL
R. E. Hitchens, BCL

Support: RR 00396

The wiring list system remains a viable tool in the implementation of hardware designs. Due to the expanded use (C-1, C-6, C-7) of TM-500 modules, the wiring list system was expanded to provide support for these modules. The system currently supports designs for Augat cards, TM-500 modules as well as a translation facility for use with design configurations other than these two layouts.

G-9. Solid-State Video Camera Characterization

Personnel: J. S. Massey, BCL
G. J. Blaine, BCL
V. W. Gerth, Jr., BCL

Support: RR 00396

In recent years, television cameras with solid-state imagers have become commercially available and economical. The imagers in these cameras use charge transfer technology, such as charge coupled devices (CCD) or charge injection devices (CID), to obtain an image. Lack of phosphor burning, short image lag, and relative absence of shading are among the potential advantages of these cameras over those with vacuum-type sensors.

Several CCD and CID cameras have been introduced recently which also have resolution approaching that of standard television devices. Thus, there is reason to believe that the unique characteristics of these cameras make their use in biomedical imaging systems desirable.

A General Electric Model TN-2500 solid-state camera has been used for several image acquisition experiments (B-16, F-4, G-14). The GE imager utilizes a CID array of 244 by 248 elements. The imager array is scanned at TV frame rates and each element is sampled and digitized to a resolution of 8 bits. The camera unit provides digital outputs for data and control.

Although parameter definitions and measurement techniques are standardized for vacuum-type sensors, comparable documentation of the recently available solid-state imaging devices is not available. Successful application of the CID or CCD devices depends on an adequate characterization of properties such as spectral sensitivity, dynamic response, uniformity, and intensity. Work has been initiated to define the parameters relevant to a variety of biomedical application areas and determine appropriate measurement techniques.

G-10. DNA Restriction Mapping Studies

Personnel: V. W. Gerth, BCL
G. J. Blaine, BCL
J. G. Dunham, BCL
A. J. Gray, BCL
J. S. Massey, BCL
M. V. Olson, Ph.D., Genetics
S. R. Prothero, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
Washington University

The objective of this activity is to construct a restriction map of yeast DNA sequences that is precisely catalogued with respect to the genomic origins of each clone. This map could be expected to be a valuable resource for a wide variety of experiments.

Analysis of the yeast genome could also be used as a rigorous proving ground for the coupling of automated methods of data acquisition and analysis to the simple experimental procedure of displaying restriction digests on electrophonetic gels. This strategy, in turn, offers promise for bringing large-scale problems such as the restriction mapping of extremely complex mammalian chromosomes within reach.

Any presently forseeable method of physically mapping eukaryotic chromosomes will have to depend upon identifying overlapping DNA sequences in a pool of cloned recombinant DNA molecules. Currently-used methods, such as DNA-DNA hybridization, are ill-suited to large problems because the overlaps must be identified sequentially and because of the large amount of time required to determine each overlap.

The alternative procedure proposed by this project uses the simpler method of displaying restriction digests on electrophonetic gels to obtain independent data on a large number of clones. This is followed by a computer-assisted topological analysis of the results.

The basic data acquisition problem will be to estimate the sizes of Eco RI fragments in approximately 3000 clones. This will require quantifying the mobilities of approximately 5×10^4 fragments on 500 separate gels. Precision of the gel reading is crucial, since pattern recognition methods will be used for data reduction. Hand measurement methods will not provide the necessary precision, and are also too time-consuming. Reasonably-priced conventional gel scanners also have problems with precision, since sample and reference gel lanes must be independently scanned and the resulting data aligned afterwards. In addition, such systems involve even more human labor than hand measurement.

Therefore we propose to construct an automated image-acquisition system specifically designed to interpret photographs of gels on which restriction digests of DNA samples have been analyzed. This system would provide complete automation of the data acquisition, allow computer assisted human editing of the results, and output the fragment-size data in machine-readable form for the topologic analysis by computer.

Preliminary image acquisition experiments have been conducted and a system configuration has been proposed. Experiments conducted using a solid-state video camera (G-10) indicated that a minimum resolution of 1024 elements per gel-lane would be required. Since the video camera's resolution is only 248 elements in one direction, a linear array (resolutions up to 1728 elements are currently available) and stage arrangement are proposed. Attempts were made to read data directly from the gels, since the photographic process could conceivably introduce distortions which might affect the measurements. However, the low level of fluorescence emitted by the dyed gel under ultraviolet light was insufficient to obtain good data from the solid state imager. Backlighted photographic negatives were found to provide adequate light intensity and have the added advantage of being easy to handle and archive.

The proposed system configuration is based on an LSI-11 microcomputer for data acquisition, and fragment analysis. A graphics terminal would facilitate interactive editing of results by the investigator. The resulting analyses of fragment sizes would be communicated to the computing center for topological analysis.

VI. INDUSTRIAL COLLABORATION

One of the goals of the Biomedical Computer Laboratory is to foster the commercial development of useful medical computer systems. Industrial collaboration provides an additional outlet for laboratory developments and benefits the staff by keeping it abreast of the practical considerations of reliability, maintainability, and cost. Progress being made in this important phase of the laboratory's activities is summarized here.

A. Arrhythmia Monitoring. Longstanding collaboration (PR 15, VI-A) with the Mennen-Medical Company (formerly Mennen-Greatbatch) continues in the areas of algorithm and experience sharing of the new QRS detector/delineator (A-1). Concepts originally tested at BCL in a Holter-tape processing environment have been applied to Mennen's monitoring system where they are now undergoing evaluation in the real-time environment. (BCL personnel: K. W. Clark, C. N. Mead, L. J. Thomas, Jr.)

B. Collaborative Drug Study. Following FDA approval of the experimental design, a research project was begun in 1976 to evaluate the safety and efficacy of a beta-adrenergic antagonist, LB-46, on ventricular irritability (PR 15, VI-B). The study was underwritten by Sandoz-Wander, Inc., developer of LB-46. Patients were recruited at the Jewish Hospital of St. Louis. The study protocol was a double-blind crossover, against placebo, of 20 ambulatory patients with a qualifying average-PVC rate of more than 20 PVCs/hr detected in a 24-hour baseline Holter recording. In addition to the relevant clinical observations and laboratory tests, a total of seven 24-hour Holter tapes per patient were collected and analyzed on the Argus/H or Argus/2H arrhythmia analysis systems. The beat-by-beat results are now undergoing biostatistical analysis. (BCL personnel: K. W. Clark, K. A. Madden, J. P. Miller, G. C. Oliver, L. J. Thomas, Jr.)

C. Exportation of Argus/2H Technology. Through a formal agreement between Washington University (WU) and Cardio-Bionic-Scanning-Incorporated (CBS), BCL personnel have consulted for CBS to Digital Equipment Corporation (DEC) for a feasibility study to be offered by DEC to CBS for developing at DEC a high-speed Holter-tape processing system which would utilize much of the technology developed for the Argus/2H arrhythmia analysis system. The feasibility study was completed, and BCL reviewed it favorably but with minor reservations. The WU-CBS agreement could continue into an implementation phase at the option of CBS, which is now reviewing the financial feasibility of the project. (BCL Personnel: K. W. Clark, R. E. Hitchens, C. N. Mead, S. M. Moore, L. J. Thomas, Jr.)

VII. TRAINING ACTIVITIES

During the year the Biomedical Computer Laboratory engaged in the following training activities:

Introductory MUMPS Programming Course for Beginners, Fall 1979.

A high-level programming language (Massachusetts General Hospital Utility Multi-Programming System - MUMPS), especially well suited for medical information systems and other textual and database applications, was presented by Joel Achtenberg, A.B. An Interactive MUMPS teaching program and access to a computer which supports Standard MUMPS were provided for laboratory exercises.

Attending the course were:

Alex Barnett, B.A.	Computer Science
Matthew Bodner, B.A.	The Jewish Hospital
Philip Burke, B.S.	Psychiatry
David Chi, M.S.	Neurology
Barbara Clark, B.S.	Surgery, Wohl Hospital
Lisa Clement	Diabetes Education Center
Seymour Fox, M.D.	Radiation Oncology
Donna Gross, M.S.W.	Social Work, Washington University
Ronald W. Hagen, M.S.	Biomedical Computer Laboratory
Wardell J. Hardy, A.A.S.	Clinical Research Center
Millard F. Johnson, M.L.S.	Medical School Library
Patricia Kane, M.L.S.	Medical School Library
Stephen A. Klem, A.B.	WUMS I Medical Student
Arthur M. Krieg, B.S.	WUMS I Medical Student
Kathleen A. Madden, A.B.	Biomedical Computer Laboratory
Jane McBride	Radiation Oncology
Yoshi S. Matsumoto	Medical School Library
Anneliese Pelech, R.N.	The Jewish Hospital
Michael A. Province, M.A.	Biomedical Computer Laboratory
Linda Rahmoller, A.A.S.	The Jewish Hospital
Polly E. Raith	Biomedical Computer Laboratory
Howard W. Renz	Pre-med Student
Steven Robinson, A.B.	Medical School Library
Loretta Stucki, M.S.	Medical School Library
Marcia Tenenbaum, B.S.	Internal Medicine
Patricia K. Thompson, B.S.	Metabolism
Eufaula Thornton	Biomedical Computer Laboratory
Ron Tissier, Ph.D.	Radiation Oncology
Deborah A. Valenzuela	Glaucoma Center
Carol M. Wincek, B.A.	Psychiatry

VIII. SEMINARS

During the year the following seminars were sponsored by the Biomedical Computer Laboratory:

"A Personal Philosophy of Data Systems" or "Why MUMPS?" or "That's a Helluva Way to Use a Computer" July 12, 1979	Mr. David A. Bridger Department of Pathology St. Louis University Medical School St. Louis, Missouri
"Series 3200 and Series 16 Minicomputer Systems" August 23, 1979	Mr. Arthur Prichard Computer Systems Division Perkin-Elmer St. Louis, Missouri
"Acquisition and Processing of the Visual Evoked Response" October 31, 1979	Mr. James K. Montrose Biomedical Computer Laboratory and Department of Electrical Engineering Washington University St. Louis, Missouri
"Performance Bounds for Noiseless Source Coding" April 25, 1980	Dr. James G. Dunham Department of Electrical Engineering Washington University St. Louis, Missouri
"Automated Film Developer for Time-Lapse Cinemicrographs" May 12, 1980	Mr. Steve Von Rump Department of Electrical Engineering Washington University St. Louis, Missouri

IX. PUBLICATIONS AND ORAL PRESENTATIONS

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X. MONOGRAPHS AND WORKING NOTES

The Biomedical Computer Laboratory's Monograph Series was established to systematize the many reports, reprints, program descriptions and other documents written at BCL or supported in part by the Laboratory's facilities or staff.

A forum, much less formal than our monograph series, has been instituted to serve as a repository for materials such as: research notes, system and component documentation, technical survey notes and pre-publication drafts. A Working Note File is maintained for access by anyone associated with the Washington University Computer Labs. Distribution for outside use can be made available with the consent of the contributor.

Monographs

Following is a list of the monographs published by BCL during the past year. Copies of the complete index to the Monograph Series are available on request.

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366	Zimmerman, J.	Resource Societies for Computer Applications in Health Care	11/79
367	Arnzen, R. J.	A User's Guide to the Universal Storage Device (USD)	7/79
368	Montrose, J. K.	VER System Users Manual	9/79
369	Cox, Jr., J. R. Gerth, Jr., V. W.	U.S. Patent #4,044,240 - Tomography System Having an Ultra High Speed Processing Unit	8/77
370	Brandenburger, G. Hitchens, R. E.	PC-Fortran-Callable Versatec Plotter Subroutines for Graphics, Text, and Grey-Scaled Images	10/79
371	Montrose, J. K. Browder, M. W. Blaine, G. J.	VER System - Technical Reference Manual	2/80

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372	Thomas, Jr., L. J. Clark, K. W. Mead, C. N. Ripley, K. L. Spenner, B. F. Oliver, Jr., G. C.	Automated Cardiac Dysrhythmia Analysis	9/79
373	Montrose, J. K.	Acquisition and Processing of the Visual Evoked Response	10/79
374	Mead, C. N. Clark, K. W. Potter, S. J. Moore, S. M. Thomas, L. J., Jr.	Development and Evaluation of a New QRS Detector/Delineator	11/79
375	Mead, C. N. J-S Cheng Hitchens, R. E. Spenner, B. F. Thomas, L. J., Jr.	Recent Progress in Frequency-Domain Analysis of the ECG	11/79
376	Vemula, R.	A Study of Human Throat-Wall and Vocal Tract from Input/Output Measurements	12/79
377	Narayan, P. Snyder, D. L.	The Two User Cutoff Rate for an Asynchronous and a Synchronous Multiple Access Channel are the Same	12/79
378	Hermes, R. E. Arthur, R. M. Thomas, Jr., L. J. Geselowitz, D. B. Oliver, G. C.	Status of the American Heart Association Database	12/79
379	Klepper, J. R.	Ultrasonic Computed Tomography: Physical Acoustics of Quantitative Imaging	5/80

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380	Ter-Pogossian, M. M. Klein, M. S. Markham, J. Roberts, R. Sobel, B. E.	Regional Assessment of Myocardial Metabolic Integrity In Vivo by Positron-emission Tomography with ^{11}C-labeled Palmitate	2/80
381	Mead, C. N. Moore, S. M.	A Detection Algorithm for Multiform Premature Ventricular Contractions	3/80
382	Brandenburger, G. H. Klepper, J. R. Miller, J. G. Snyder, D. L.	Ultrasonic Parameter Anisotropy and Its Effects in Computed Tomography, Part I	5/80
383	Hartz, R. K. Hart, Jr., W. M.	A Perimetrist's Manual for the Visual Field Recording Instrument	6/80

Working Notes

Following is an index of notes submitted during the current reporting period.

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1	Clark, K. W. Mead, C. N.	A Generalized Treatment of the Argus for Placing QRS Complexes Within Family Clusters	2/80
2	Gray, A. J.	Silver Grain Counter Personnel, Collaborators, BCL Administration	2/80
3	Browder, M. W.	Operating Procedure for the PC-1200 Based VER Processing System	5/80
4	Browder, M. W.	VER 9-Track Transfer Tape Data Format	6/80
5	Hermes, R. E.	American Heart Association Database	6/80

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6	Hartz, R. K.	MC6800 Software for the Visual-Fields Data Acquisition System	6/80
7	Prothero, S. R.	PDP-11/LEXIDATA Software	6/80
8	Gray, A. J.	Automatic Stage Control Processor Documentation Package	7/80