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CT of the Heart

Second Edition

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U. Joseph Schoepf
Editor

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Editor
U. Joseph Schoepf
Department of Radiology
Center for Advanced Imaging Research (CAIR)
Medical University of South Carolina
Charleston, SC
USA

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This book is dedicated to my mother Ursula Schoepf and my late father, Josef Schoepf.

Foreword to the First Edition

Radiologic technology has made dramatic advances in the last 25 years, and none have been more impressive than those in computed tomography (CT). The progress in the speed of obtaining images, computing, postprocessing, and spatial resolution has been incredible. The result is that CT has moved from displaying purely morphologic information to providing valuable physiologic data as well. Whether with electron beam or multidetector-row CT, advances are impressive and nowhere have the applications been more useful and dramatic than in the heart.

This multiauthored book, *CT of the Heart*, edited by U. Joseph Schoepf, MD, is a splendid rendition of the state-of-the-art in CT imaging of the heart; however, where appropriate, it also features comparisons with other technical approaches, such as magnetic resonance and ultrasound. The contributors are leading radiologists, cardiologists, physicists, engineers, and basic and clinical scientists from Europe, the United States, Israel, and Japan.

The entire contents are meticulous and comprehensive, from the introduction about the past, present, and future of CT of the heart, through the technical underpinning of the method and the various clinical, physiologic, and pathologic applications of CT in studying the heart.

This book fills an immense need, particularly at a time when cardiac screening with CT, whether one agrees with this practice or not, is a reality. Furthermore, with the rapid increase of aging populations in the industrialized world, noninvasive diagnostic approaches are increasingly needed. As technology continues to advance and applications of CT to heart studies expand, it is my hope that the editor will bring this book up to date with a new edition.

Alexander R. Margulis, MD, DSc (HON)
Clinical Professor of Radiology
Weill Medical College of Cornell University,
New York, NY, USA

Foreword

CT imaging of the heart and coronary vessels has emerged over the past two decades as one of the most important and dynamic advances in medicine. Heart disease is the leading cause of death in the United States and worldwide, challenging health systems and health providers on how best to diagnose and manage their patients. CT imaging helps address these questions through the remarkable and important information it provides about both cardiovascular anatomy and function.

The first edition of *CT of the Heart: Principles and Applications* edited by U. Joseph Schoepf was excellent. The book was very well received and widely used. Dr. Schoepf chose a multiauthor format that allowed him to invite key leaders in each aspect of the subject to contribute their special knowledge—physicists, engineers, radiologists, cardiologists, and others. Their presentations were outstanding—richly illustrated and put in appropriate context with other methods.

The second edition of *CT of the Heart* promises to build on the excellence of the first edition by maintaining the strategy of selecting the most expert people as authors. To this end, Dr. Schoepf has maintained the multiauthor format in the second edition, now inviting over 170 people from around the globe as contributors. The authorship list is a true "Who's Who" of people working in the field.

Two things happen over time that make new editions of even the most classic medical texts vital and important. These are implicit in the subtitle of the first edition of *CT of the Heart* and are advancements in the science and technology underlying the subject and advancements in the accumulated knowledge about the role and efficacy of clinical applications. In the decade between editions, it is fair to say that the pace of technology development has steadily increased and that new applications have been added to clinical practice. Dr. Schoepf and his coauthors address these important advances in the second edition. The discussion of each topic is designed to bring it up to date, and several new chapters have been added to cover new areas of technology development and clinical application. As in the first edition, the discussions are meticulous and comprehensive.

Another feature of *CT of the Heart* that will be useful to readers is the separation of chapters into categories of "Where We Were," "Where We Are," and "Where We Are Going." Too often in textbooks, there is not a clear separation of material covering topics recognized as well established versus emerging topics that are important in comprehensive understanding of a subject but not yet in routine clinical use. The 14 chapters in the section on "Where We Are Going" bespeak the dynamic advances being made in CT imaging. Topics in this section include new approaches to anatomic and functional applications such as new approaches to myocardial perfusion imaging but also the potential roles of radiomics, big data, and machine learning.

CT of the Heart will be invaluable for students and trainees seeking to learn the subject as well as established physicians looking for definitive reference information or for ideas about how to continue to advance their practices. Since the second edition has the same attributes that made the first edition a trusted resource, it will soon be regarded in the same way. Dr. Schoepf and his coauthors are to be congratulated for producing such a high-quality and timely text.

James H. Thrall, MD
Chairman Emeritus, Department of Radiology
Massachusetts General Hospital
Boston, MA, USA

Distinguished Taveras Professor of Radiology
Harvard Medical School
Boston, MA, USA

Preface

Ποταμοῖσι τοῖσιν αὐτοῖσιν ἐμβαίνουσιν, ἕτερα καὶ ἕτερα ὕδατα ἐπιρρεῖ… – Herakleitos

More than a decade has passed since the publication of the first edition of *CT of the Heart*. And what a ride it's been since then! From the perch of today's technology, with lightning-fast acquisition speeds and temporal resolution, massive tube power, yet gentle techniques, the evolution could not have been more dramatic. Back then we were mostly still living in the dark ages of 16-slice multidetector-row CT technology, with 64-slice CT faintly on the horizon.

While we have been experiencing the evolution of cardiac CT as a continuum, for many the introduction of 64-slice CT technology constitutes the pivotal breaking point in history, whence the clinical use of cardiac CT became more broadly established for the first time. In the subsequent years, we all expected a revolution, a wildfire to happen, with cardiac CT ensconcing itself rapidly, profoundly, and irrevocably in all arenas of cardiovascular medicine. It did not happen quite as fast as many had betted on, causing a degree of disillusionment in some quarters. After all, it may not be a bad thing that not every latest flash in the pan gets embraced by mainstream medicine overnight.

But then something quite rare and precious happened; the field of believers in this technology came together and, in a manner unprecedented in medical imaging, piece by piece built the evidence that incrementally drove this test to new heights and today forms the foundation for the ever-growing importance of cardiac CT. In fact, we submit that cardiac CT may be considered a beacon, a blueprint, and prime example of how the value of a medical test can be unequivocally proven and supported via the generation of high-level evidence, a formidable challenge that the field of medical imaging has mostly unsuccessfully grappled with to date. This is what this book is about; while in the first edition we mainly investigated a fascinating new instrument looking for an application, we now have a vast realm of guideline-driven, robust, and beneficial clinical applications that are enabled by an enormous and ever-growing field of technology. Accordingly, the focus has shifted from a technology-centric to a more patient-centric appraisal. While the specifications and capabilities of the CT system itself remain front and center as the basis for diagnostic success, much of the benefit derived from cardiac CT today comes from avant-garde technologies enabling enhanced visualization, quantitative imaging, and functional assessment, along with exciting deep learning, and artificial intelligence applications. Long have we passed the stage of a mere tool for noninvasive coronary artery stenosis detection in the chest pain diagnostic algorithms; cardiac CT has proven its value for uses as diverse as personalized cardiovascular risk stratification, prediction, and management, diagnosing lesion-specific ischemia, guiding minimally invasive structural heart disease therapy, and planning cardiovascular surgery, among many others.

In the Preface to the first edition of *CT of the Heart*, we stated that we do not claim to have all the answers. That is still the case; but we have vastly more answers and enough to know that cardiac CT is here to stay and bound to occupy the space that we originally envisioned. In some more regulated and resource-conscious economies, we already see cardiac CT positioned as the entrance test and gatekeeper to any type of chest pain work-up, invasive or not. However, also in less progressive, more entrenched, and conflicted healthcare systems around the globe, this test is now quickly gaining ground and will even more so with newer generations of healthcare providers who are less enamored with outdated testing strategies of the past.

Like the first edition, the second edition of *CT of the Heart* is again a snapshot of the *status quo*, of the current state-of-the-art, and of a success story in the care for our patients which still keeps rapidly evolving. Yet, we have a much clearer view now of what we have accomplished, where we are, and where we are going.

While the first edition was the work of many, the second edition is the result of the work of even more. An astounding array of the great houses in cardiac imaging, giants in the field, came together to present our readers with the most comprehensive, coherent, up-to-date, and in-depth review of cardiac CT principles and applications. We are grateful beyond limits to this exalted, respected group of experts who poured their genius into this tome. Finally, this work would not have come to fruition without the invaluable help of Taylor M. Duguay and Dante Giovagnoli in our lab and Margaret Burns of Springer, who so skillfully and deftly steered the production of this second edition. We hope that this work will inspire and guide current and future leaders in healthcare in their quest to optimally harness the powers of a disruptive, amazing technology, to the benefit of our patients worldwide.

Charleston, SC, USA U. Joseph Schoepf

Contents

Contributors

Suhny Abbara, MD, FACR, FSCCT Department of Radiology, Cardiothoracic Imaging Division, UT Southwestern Medical Center, Dallas, TX, USA

Moritz H. Albrecht, MD Department of Diagnostic and Interventional Radiology, University Hospital Frankfurt, Frankfurt am Main, Germany

Hatem Alkadhi, MD, MPH, EBCR Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich, Switzerland

Thomas Allmendinger, PhD Department of Computed Tomography, Siemens Healthcare GmbH, Forchheim, Germany

Amadeus Altenburger, Dr. med Department of Diagnostic and Interventional Radiology and Neuroradiology, Klinikum Augsburg, Augsburg, Germany

Kweku Appau, MD Department of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

Christoph Artzner, MD Department of Radiology, Duke University Medical Center, Durham, NC, USA

Department of Diagnostic and Interventional Radiology, University of Tuebingen, Tubingen, Germany

Anil Attili, MD Department of Radiology, Division of Cardiothoracic Radiology, University of Michigan, Ann Arbor, MI, USA

Adefolakemi Babatunde, MD Cardiovascular Division, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA

Fabian Bamberg, MD, MPH Department of Diagnostic and Interventional Radiology, University of Tuebingen, Tubingen, Germany

Gorka Bastarrika, MD, PhD, EBCR Cardiothoracic Imaging Division, Department of Radiology, Clínica Universidad de Navarra, Pamplona, Spain

Richard R. Bayer II, MD Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA

Raveen Bazaaz, MD Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Hans-Christoph R. F. Becker, MD Department of Radiology, Stanford University, Stanford, CA, USA

Daniel Berman, MD Department of Imaging and Medicine and the Burns Allen Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Philipp Blanke, MD Department of Radiology, University of British Columbia, Vancouver, BC, Canada

Daniel T. Boll, MD Department of Radiology, University of Basel, Basel, Switzerland

Marques L. Bradshaw, MD Department of Radiology and Radiological Sciences, Vanderbilt University School of Medicine, Nashville, TN, USA

Herbert Bruder, PhD Department of Computed Tomography, Siemens Healthcare GmbH, Forchheim, Germany

Patricia Carrascosa, MD, PhD Department of Cardiovascular Imaging, Diagnóstico Maipú, Buenos Aires, Argentina

Damiano Caruso, MD Department of Radiological Sciences, Oncological and Pathological Sciences, University of Rome "Sapienza", Latina, Italy

Csilla Celeng, MD Department of Radiology, Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Siyu Chen, BS Department of Radiologic Imaging, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center of Cardiovascular Diseases, Beijing, China

Yundai Chen, MD, PhD Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Department of Cardiology, People's Liberation Army General Hospital, Beijing, China

Leonid Chepelev, MD, PhD Department of Radiology, University of Ottawa Faculty of Medicine, Ottawa, ON, Canada

Ottawa Hospital Research Institute, Ottawa, ON, Canada

Salvatore A. Chiaramida, MD Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA

Yeon Hyeon Choe, MD, PhD Department of Radiology, HVSI Imaging Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Byoung Wook Choi, MD, PhD Department of Radiology, Yonsei University School of Medicine, Severance Hospital, Seoul, South Korea

Jin-Ho Choi, MD Division of Cardiology, Department of Medicine (J-H C), Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Shahryar M. Chowdhury, MD, MSCR Division of Pediatric Cardiology, Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA

Adriaan Coenen, MD Departments of Radiology and Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands

Andrew Crean, BSc, BM, MRCP, MSc, FRCR, MPhil Department of Cardiology, Ottawa Heart Institute, University of Ottawa, Ottawa, ON, Canada

Marco Das, MD, PhD Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands

Carlo N. De Cecco, MD, PhD Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Domenico De Santis, MD Department of Radiological Sciences, Oncological and Pathological Sciences, University of Rome "Sapienza", Latina, Italy

Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Annemarie M. den Harder, MD, PhD Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

Karin E. Dill, MD Department of Radiology, UMass Medical Center, Worcester, MA, USA

Ian R. Drexler, MD, MBA Department of Radiology, Weill Cornell Medicine, New York, NY, USA

Taylor M. Duguay, BS Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Ullrich Ebersberger, MD Department of Cardiology and Intensive Care Medicine, Heart Center Munich-Bogenhausen, Munich, Germany

Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Heidi A. Edmonson, PhD Department of Radiology, Mayo Clinic, Rochester, MN, USA

Marwen Eid, MD Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Ahmed Hamdy, MD Department of Radiology, Mie University Hospital, Tsu, Japan

Christian D. Eusemann, PhD Department of Collaborations, Siemens Medical Solutions USA, Inc., Malvern, PA, USA

Lloyd M. Felmly, MD Department of Surgery, Division of Cardiothoracic Surgery, Medical University of South Carolina, Charleston, SC, USA

Gudrun M. Feuchtner, MD Department of Radiology, Innsbruck Medical University, Innsbruck, Austria

Aloke V. Finn, MD CVPath Institute, University of Maryland, Gaithersburg, MD, USA

Thomas G. Flohr, PhD Department of Computed Tomography, Siemens Healthcare GmbH, Forchheim, Germany

Kunihiko Fukuda, MD Department of Radiology, The Jikei University School of Medicine, Tokyo, Japan

Michael Gebhard, MD Department of Diagnostic and Interventional Radiology and Neuroradiology, Klinikum Augsburg, Augsburg, Germany

Lucas L. Geyer, MD Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Institute for Clinical Radiology, Ludwig-Maximilians-University Hospital Munich, Munich, Germany

Brian B. Ghoshhajra, MD, MBA Division of Cardiovascular Imaging, Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA

Cardiac MR PET CT Program, Massachusetts General Hospital, Boston, MA, USA

Frank Gijsen, PhD Department of Biomedical Engineering, Erasmus University Medical Center, Rotterdam, The Netherlands

Harold Goerne, MD Department of Radiology, Cardiothoracic Imaging, UT Southwestern Medical Center, Dallas, TX, USA

Orly Goitein, MD Department of Diagnostic Imaging, Chaim Sheba Medical Center, Ramat Gan, Israel

Katharine Grant, PhD Siemens Medical Solutions USA, Inc., Malvern, PA, USA

Daniel B. Green, MD Department of Radiology, Weill Cornell Medicine, New York, NY, USA

David Gregg, MD Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA

B. Kelly Han, MD Department of Advanced Congenital Cardiac Imaging, Minneapolis Heart Institute and the Children's Hospitals and Clinics of Minnesota, Minneapolis, MN, USA

Thomas Henzler, MD Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany

Anthony M. Hlavacek, MD Department of Pediatrics, Division of Pediatric Cardiology, Medical University of South Carolina, Charleston, SC, USA

Udo Hoffmann, MD Department of Cardiovascular Imaging, Massachusetts General Hospital, Boston, MA, USA

Jin Hur, MD, PhD Department of Radiology, Yonsei University School of Medicine, Severance Hospital, Seoul, South Korea

Lynne M. Hurwitz, MD Department of Radiology, Duke University Medical Center, Durham, NC, USA

Gregory Jackson, MD Department of Cardiology, Medical University of South Carolina, Charleston, SC, USA

Brian Jacobs, BS Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Michael A. Kadoch, MD Department of Radiology, University of California, Davis, CA, USA

Steffen Kappler, Dr. rer. Nat Department of Computed Tomography, Siemens Healthcare GmbH, Forchheim, Germany

Ella A. Kazerooni, MD, MS, FACR Department of Radiology, Division of Cardiothoracic Radiology, University of Michigan, Ann Arbor, MI, USA

Sung Mok Kim, MD Department of Radiology, HVSI Imaging Center, Heart Vascular Stroke Institute, Seoul, South Korea

Kakuya Kitagawa, MD, PhD Department of Radiology, Mie University Hospital, Tsu, Japan

Friedrich Knollmann, MD, PhD Department of Radiology, UCDavis Health, Sacramento, CA, USA

Brian S. Ko, MBBS (Hons), PhD Department of Medicine Monash Medical Centre (MMC), Monash Cardiovascular Research Centre, MonashHEART, Monash Health and Monash University, Melbourne, Australia

James M. Kofler, PhD Department of Radiology, Mayo Clinic, Jacksonville, FL, USA

Madeleine Kok, MD, PhD Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands

Frank D. Kolodgie, PhD CVPath Institute, Gaithersburg, MD, USA

Márton Kolossváry, MD Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Eli Konen, MD Department of Diagnostic Imaging, Chaim Sheba Medical Center, Ramat Gan, Israel

B. Krauss, PhD Siemens Healthcare GmbH, Forchheim, Germany

Shaw Hua Kueh, MBChB Department of Radiology, University of British Columbia, Vancouver, BC, Canada

Joan M. Lacomis, MD Department of Radiology, Thoracic Imaging Division, University of Pittsburgh Medical Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Scott P. Landreth Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Hwa Yeon Lee, MD, PhD Smile Radiologic Clinic, Seoul, South Korea

Jongmin Lee, MD, PhD Department of Radiology, Kyungpook National University, School of Medicine, Daegu, South Korea

Nam Ju Lee, MD Department of Radiology, Mayo Clinic, Rochester, MN, USA

Alan C. Legasto, MD Department of Radiology, Weill Cornell Medicine, New York, NY, USA

Jonathon A. Leipsic, MD Department of Radiology, St. Paul's Hospital, Providence Healthcare, Vancouver, BC, Canada

Shuai Leng, PhD Department of Radiology, Mayo Clinic, Rochester, MN, USA

John R. Lesser, MD, FACC, FAHA Minneapolis Heart Institute Foundation, Minneapolis, MN, USA

Virginia W. Lesslie, BS Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

David C. Levin, MD Department of Radiology, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Ana Paula S. Lima, MD Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA

Fay Y. Lin, MD Department of Radiology, NewYork-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA

Harold Litt, MD, PhD Department of Radiology, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

Sheldon E. Litwin, MD Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA

Bin Lu, MD Department of Radiologic Imaging, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center of Cardiovascular Diseases, Beijing, China

Guang Ming Lu, MD Department of Medical Imaging, Jinling Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, China

Manoj Mannil, MD, MSc Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich, Switzerland

Mohamed Marwan, MD Department of Medicine, Cardiology and Angiology, Universitätsklinikum Erlangen, Erlangen, Germany

Pál Maurovich-Horvat, MD, PhD, MPH Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest, Hungary

C. H. McCollough, PhD Department of Radiology, Mayo Clinic, Rochester, MN, USA

Felix G. Meinel, MD Department of Diagnostic and Interventional Radiology, Rostock University Medical Center, Rostock, Germany

Nandini (Nina) M. Meyersohn, MD Division of Cardiovascular Imaging, Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA

Casper Mihl, MD, PhD Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands

James K. Min, MD Department of Radiology, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA

John F. Mooney, MBB Department of Radiology, University of British Columbia, Vancouver, BC, Canada

Hiroyoshi Mori, MD CVPath Institute, Gaithersburg, MD, USA

Pamela B. Morris, MD Seinsheimer Cardiovascular Health Program, Department of Medicine and Cardiology, Medical University of South Carolina, Charleston, SC, USA

Giuseppe Muscogiuri, MD Centro Cardiologico Monzino, IRCCS, Milan, Italy

John W. Nance, MD Department of Radiology, Medical University of South Carolina, Charleston, SC, USA

Koen Nieman, MD, PhD Stanford University, School of Medicine, Cardiovascular Institute, Stanford, CA, USA

Iclal Ocak, MD Department of Radiology, Thoracic Imaging Division, University of Pittsburgh Medical Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Maksymilian P. Opolski, MD, PhD Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland

Karen G. Ordovas, MD, MAS Department of Radiology, University of California San Francisco, San Francisco, CA, USA

Kotaro Ouchi, MD, PhD Department of Radiology, The Jikei University School of Medicine, Tokyo, Japan

Gert Jan Pelgrim, PhD Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Laura J. Pierce, MPA, RT (CT) Department of Radiology, Duke University School of Medicine, Durham, NC, USA

Todd Pietila Materialise USA Biomedical Engineering, Plymouth, MI, USA

Gianluca Pontone, MD, PhD, FESC, FSCCT Centro Cardiologico Monzino, IRCCS, Milan, Italy

Andrew N. Primak, PhD Department of Diagnostic Imaging, Siemens Healthineers, Malvern, PA, USA

Gregorio Rábago, MD Department of Cardiac Surgery, Clínica Universidad de Navarra, Pamplona, Spain

Mark Rabbat, MD, FSCCT Department of Medicine, Division of Cardiology, Loyola University Chicago, Chicago, IL, USA

Department of Medicine, Division of Cardiology, Edward Hines Jr. VA Hospital, Hines, IL, USA

Prabhakar Rajiah, MBBS, MD, FRCR Department of Radiology, Cardiothoracic Imaging Division, UT Southwestern Medical Center, Dallas, TX, USA

Matthias Renker, MD Department of Cardiology, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany

Xinshuang Ren, MD Department of Radiologic Imaging, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center of Cardiovascular Diseases, Beijing, China

Asim Rizvi, MD Department of Radiology, Dalio Institute of Cardiovascular Imaging, NewYork-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA

Department of Radiology, Mayo Clinic, Rochester, MN, USA

Sebastian Rogowski, MD Department of Cardiology and Intensive Care Medicine, Heart Center Munich-Bogenhausen, Munich, Germany

Hadi Mirhedayati Roudsari, MD Department of Radiology, NewYork-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA

Alan Rozanski, MD Department of Cardiovascular Medicine, Gagnon Cardiovascular Institute, Morristown Medical Center, Morristown, NJ, USA

The Division of Cardiology, Mount Sinai St. Luke's Hospital, Mount Sinai Heart, New York, NY, USA

Geoffrey D. Rubin, MD, MBA Department of Radiology, Duke University School of Medicine, Durham, NC, USA

Ronen Rubinshtein, MD Department of Cardiovascular Medicine, Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

John A. Rumberger, PhD, MD Department of Cardiac Imaging, The Princeton Longevity Center, Princeton, NJ, USA

Frank J. Rybicki, MD, PhD Department of Radiology, University of Ottawa Faculty of Medicine, Ottawa, ON, Canada

Ottawa Hospital Research Institute, Ottawa, ON, Canada

Pooyan Sahbaee, PhD Siemens Medical Solutions USA, Inc., Malvern, PA, USA

Toru Sakuma, MD, PhD Department of Radiology, The Jikei University School of Medicine, Tokyo, Japan

Arnold M. R. Schilham, PhD Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

Christopher L. Schlett, MD, MPH Department of Diagnostic and Interventional Radiology, University Medical Center Freiburg, Freiburg, Germany

Bernhard Schmidt, PhD Department of Computed Tomography, Siemens Healthcare GmbH, Forchheim, Germany

Paul Schoenhagen, MD Imaging Institute, Cleveland Clinic, Lerner College of Medicine, Cleveland, OH, USA

Jan-Erik Scholtz, MD Cardiac MR PET CT Program, Massachusetts General Hospital, Boston, MA, USA

Florian Schwarz, PD Dr. med Department of Diagnostic and Interventional Radiology and Neuroradiology, Klinikum Augsburg, Augsburg, Germany

Chris Schwemmer, MSc Department of Computed Tomography, Siemens Healthcare GmbH, Forchheim, Germany

Stephanie Sellers, MSc Department of Radiology, University of British Columbia, Vancouver, BC, Canada

Michael D. Shapiro, DO Department of Medicine, Division of Cardiovascular Medicine, Oregon Health & Science University, Portland, OR, USA

James V. Spearman, MD Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

David Steflik, MD Department of Pediatrics, Division of Pediatric Cardiology, Medical University of South Carolina, Charleston, SC, USA

Arthur E. Stillman, MD, PhD Department of Radiology and Imaging Science, Emory University School of Medicine, Atlanta, GA, USA

Pal Spruill Suranyi, MD, PhD Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA

Richard A. P. Takx, MD, MSc, PhD Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

Christian Tesche, MD Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Department of Cardiology and Intensive Care Medicine, Heart Center Munich-Bogenhausen, Munich, Germany

Christian Thilo, MD Department of Cardiology, Klinikum Augsburg, Herzzentrum Augsburg-Schwaben, Augsburg, Germany

Quynh A. Truong, MD, MPH, FACC Department of Radiology, Weill Cornell Medicine, New York, NY, USA

Seth Uretsky, MD Department of Cardiovascular Medicine, Gagnon Cardiovascular Institute, Morristown Medical Center, Morristown, NJ, USA

Marly van Assen, MSc Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Department of Radiology and Radiological Science, Division of Cardiovascular Imaging, Medical University of South Carolina Charleston, SC, USA

Edwin J. R. van Beek, MD, PhD Edinburgh Imaging Facility QMRI, University of Edinburgh, Edinburgh, UK

Akos Varga-Szemes, MD, PhD Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Renu Virmani, MD CVPath Institute, Gaithersburg, MD, USA

Rozemarijn Vliegenthart, MD, PhD Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Department of Radiology and Radiological Science, Division of Cardiovascular Imaging, Medical University of South Carolina Charleston, SC, USA

Andrew Voigt, MD Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Charles S. White, MD Department of Diagnostic Radiology, University of Maryland Medical Center, Baltimore, MD, USA

Joachim E. Wildberger, MD, PhD Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands

Martin J. Willemink, MD, PhD Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

Michelle C. Williams, MBChB, PhD Edinburgh Imaging Facility QMRI, University of Edinburgh, Edinburgh, UK

Eric E. Williamson, MD Department of Radiology, Mayo Clinic, Rochester, MN, USA

Arik Wolak, MD Department of Cardiology, Shaare Zedek Medical Center, Jerusalem, Israel

Pamela K. Woodard, MD Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, USA

Junjie Yang, MD Division of Cardiovascular Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA

Department of Cardiology, People's Liberation Army General Hospital, Beijing, China

Weihua Yin, MD Department of Radiologic Imaging, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center of Cardiovascular Diseases, Beijing, China

Seung Min Yoo, MD, PhD Department of Radiology, CHA University Bundang Medical Center, Bundang, South Korea

Long Jiang Zhang, MD, PhD Department of Medical Imaging, Jinling Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, China

Mathis Zimmermann, Dipl Ing, MBA Digital Health Services, Siemens Healthineers, Malvern, PA, USA

Peter L. Zwerner, MD Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA

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Part I

Where We Were

History of Cardiac CT: A Personal Story

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John A. Rumberger

As the story goes, Wilhelm Conrad Röentgen, a physicist, was working late in his laboratory in Wurzburg, Germany, experimenting with a vacuum tube made of glass. He was using this to generate beams of electrons and wrapped the tube with black paper to avoid viewing the electric discharge occurring in the gas inside the vacuum tube. When he started his experiment, he noted that a piece of coated paper lying near the tube began to glow. He was astonished and did another experiment where he held a thick book between the tube and the paper – however, the "rays" simply passed through the book, as if totally unobstructed. When Röentgen looked at the coated paper it showed a shadowy outline of the bones in his hand. This was November 8, 1895, and the world of the "X-ray" has never looked back.

The "X-ray" has been intimately linked to the ability to see "inside" the body since the late nineteenth century; but it remained a projection image with superposition of all the densities of the tissue placed between the anode and the cathode. To separate these various tissue densities, a thin cross-sectional image would be of significant benefit as the various organs can be separated from their surrounding tissues of fat, muscle, and bone.

The birth of clinical X-ray computed tomography (CT) was not realized until about 80 years after Röentgen's discovery. At the time of this writing, an estimated 90,000 peer reviewed scientific articles have been published on or about CT. A dominant majority of these articles deal with body organs and processes that either do not move during the image acquisition or, in the case of lung imaging, when motion can be suspended long enough to get "static images." In the case of cardiac CT imaging, however it is a different story and has been a difficult challenge to image an object that is constantly moving in four dimensions and cannot be, safely, stopped. Cardiac CT and my personal involvement with cardiac CT interestingly started nearly at the same time as the development of commercial CT in general.

In the Beginning, There Was Mathematics

The story of cardiac CT, and all CT for that matter, begins with mathematics that allow us to "reconstruct" the density/tissue characteristics of an "unknown" object placed in a black box as light [or later X-ray] of known intensity is shown through. Pierre Bouguer, credited in about 1729, noted that the absorption of light through an object is directly proportional to its thickness [or path length]. Lambert later popularized this observation in a paper from 1760. August Beer discovered another light attenuation factor in 1852 noting that light absorbance was proportional to the concentrations of the attenuating "unknown object." The modern Lambert-Beer law combines these two observations and correlates the changes in light energy to both the concentration of the attenuating "unknown" object and the thickness of the unknown object. Since visible light is part of the electromagnetic energy spectrum, this can apply to the application of X-rays as well. The general application of the Lambert-Beer law to X-ray imaging is shown in Fig. 1.1.

Referring to Fig. 1.1, the unknown object of density μ represents a "pixel" [i.e., picture element] size of 1×1. If we know the incident radiation and the output radiation after passing through the unknown object, as well as the distance between these measurements, the Lambert-Beer law then provides an equation with only one unknown, i.e., μ. What if I wanted to determine the density of four unknown μ objects? I can use the Lambert-Beer law to set up four equations in four unknowns or a field of view of 2×2 pixels as shown in Fig. 1.2. However, the ability to solve pixel density resolutions of 80×80 pixels [as was used on the first-generation clinical CT scanner] was simply too daunting a task until the modern development of the computer. The "exact solutions" for the individual μ, to speed up the mathematical solutions,

J. A. Rumberger (✉)
Department of Cardiac Imaging, The Princeton Longevity Center, Princeton, NJ, USA
e-mail: jrumberger@theplc.net

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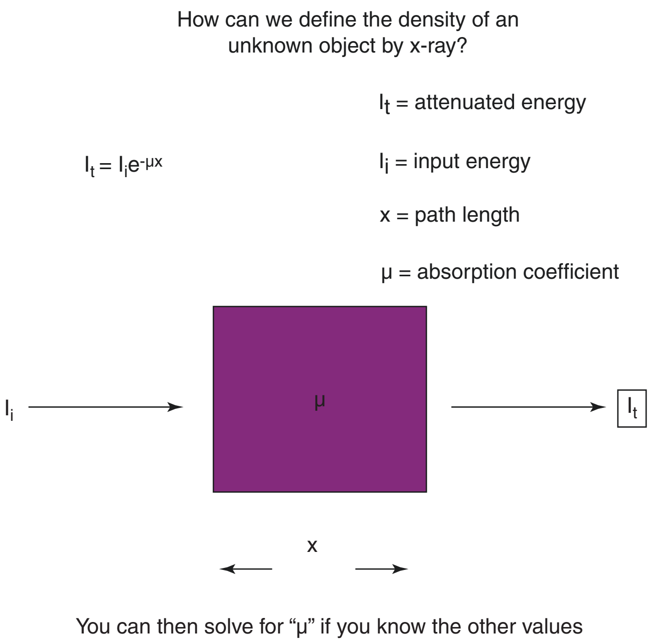

Fig. 1.1 The Lambert-Beer law applied to X-ray

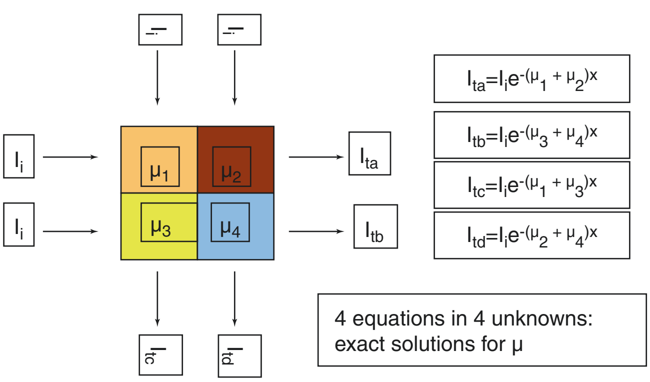

Fig. 1.2 The exact solution of the Lambert-Beer law for four unknown objects of density μ

initially involved various "iterative" methods. The final solutions reached in a series of best guesses and comparisons with the actual data. The original mathematics was part of the ART [algebraic reconstruction theory] algorithm [1].

In 1963 another physicist in South Africa, Allan Cormack, was working on improving the dose calculations used in radiation therapy planning, but knowledge of cross-sectional density distributions was required. He developed the first concept of image reconstruction from projections [2]. This became the basis for another image reconstruction called "back projection" [later improved to reduce noise at the edges of objects and called "filtered back projection"] [3].

Attainment of Reality in Clinical Medicine: The EMI Scanner

Modern X-ray CT was developed by Sir Godfrey Hounsfield while working for Electronic and Musical Industries Ltd. [EMI] in England. A prototype scanner using an X-ray tube was developed in 1969/1970 and a clinically applicable scanner installed at the Atkinson Morley Hospital in a London suburb in 1971; the first clinical results were presented in 1973 [4]. At first only the brain could be imaged due to very long acquisition times in which the patient was required to be very still [and surrounded by a water phantom]. The first clinical CT scanner in the USA was installed at the Mayo Clinic in Rochester, Minnesota, in 1973.

As an interesting personal anecdote, the engineer installing the scanner at the Mayo Clinic was named David King and had worked closely with Hounsfield in England. David King, later the founder of "calcium club" [see further discussion below] and acknowledged as the "father" of coronary artery calcium scanning, told me a story. When Hounsfield and colleagues at EMI contemplated the "world's" eventual needs for such a unique brain imaging device, they estimated that probably less than a hundred scanners would be eventually made and sold. After 1 week at the Mayo Clinic, and after performing more head/brain CT scans than had been done in the past 2 years in England, David told Godfrey – "Maybe you might want to increase your estimation of the world's need for the EMI scanner".

By 1975 a second-generation EMI scanner, the first prototype "body scanner" was introduced. Acquisition times per slice were about 20 s, and it used iterative reconstruction techniques although the much faster filtered back projection method was now established. Because of the success of the EMI scanner, many other commercially available scanners were quickly introduced by other manufacturers that, like EMI itself, eventually went under, while others such as the Picker, Siemens, and GE survived. But the die was cast. In 1979 both Hounsfield and Cormack received the Nobel Prize in Physiology and Medicine for the development of the CT scanner.

The Dynamic Spatial Reconstructor

There were several attempts to using "conventional" CT scanning in the early 1980s to study the cardiovascular system, mainly viewing patency of coronary artery bypass grafts and looking for aortic dissections [5]. Already there was a clear advantage noted in cardiac CT over the conventional M-mode/sector echocardiographic examinations and plane chest X-rays that were "state of the art" at the time for imaging of the chest and heart.

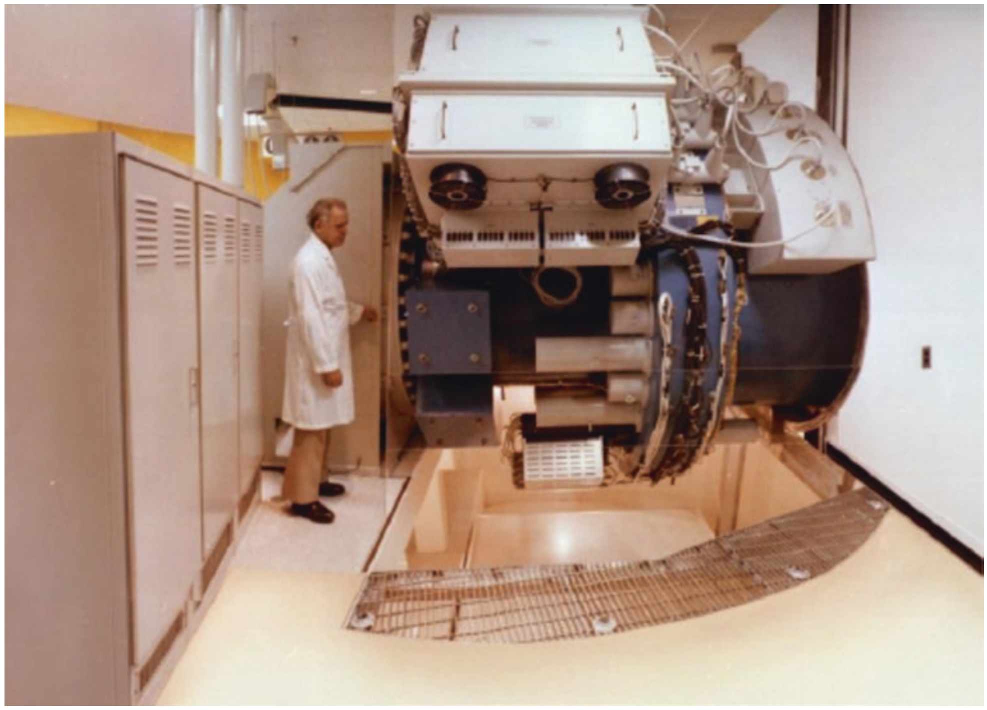

Fig. 1.3 The dynamic spatial reconstructor. (With permission of the Mayo Foundation for Medical Education and Research. All rights reserved)

The Biodynamics Research Laboratory at the Mayo Clinic had a long and storied history with aviation medicine in World War II and under the directorship of Dr. Earl H. Wood did the first human centrifuge experiments studying "G" force [i.e., gravity] effects on pilots during flight and combat. Along with the US government, they developed the first "G-suits," and after the war Dr. Wood was awarded a special commendation by President Harry S. Truman.

The idea of using X-ray CT to study the moving heart dated to the first body images produced using the EMI body scanner; but despite some success as noted by Brundage et al. [5], the spatial resolution and most importantly the temporal resolution were not sufficient for most clinical cardiac work. The idea of developing a CT scanner fast enough to make "stop action" images of the beating heart was first realized in the Biodynamics Research Laboratory where, under NIH funding, they introduced the Dynamic Spatial Reconstructor (DSR) in 1975.

The DSR was imagined as a specialized cardiac CT scanner using conventional X-rays with photomultiplier tubes and fluoroscopic projection imaging applied in a unique manner (Fig. 1.3). The original design was to use 28 pairs of X-ray sources and 28 direct line visualization fluoroscopic units. This vast array [requiring literally two floors with gantry and imaging chain] was then rotated at high speed as images of the beating heart were acquired using intra-arterial injection of iodinated contrast over a period of about 20 s. Using ART reconstruction methods, a temporal resolution of 16 msec/image could be realized as well as spatial resolution approaching 1 mm. However, only 14 sets of X-ray/fluoroscopic units were installed due to technical difficulties and funding. Later the fluoroscopic units were replaced by CCDI cameras. Image reconstruction however was arduous and could take as long as several weeks to be completed. Specialized software was developed to review and analyze the data. Countless contributions to the world of cardiac CT were introduced by the investigators working on multiple aspects of the DSR project [6–8]. I can recall at one of my earliest American Heart Association conventions as a cardiology fellow seeing the astounding video presented by Dr. Eric Ritman, the then head of the biodynamics research unit, showing detailed anatomy of adult patients in 3-D and, with time added, in 4-D. Unfortunately, the DSR was not a commercially viable enterprise and was decommissioned in 2002. By that time cardiac imaging using MDCT was developing rapidly.

Electron Beam CT

In the early 1970s, the initial applications to develop a specialized cardiac CT scanner given to the NIH were of two distinctly different designs. The X-ray tube/fluoroscopic unit design as noted above was eventually used for the DSR. However, another design using scanning electron beams was discussed.

The scanning electron beam approach eventually proved to be the superior design for practical clinical applications and for commercial product success. However, this required many years in development. Two early designs, one by Iinuma et al. [9] at JEOL, a Japanese manufacturer of electron microscopes, and by Haimson [10] resulted in prototype machines but were abandoned. Published in the same issue as Reference [8], citing the initial DSR results, was a third design, originating with Dr. Douglas Boyd [11, 12]. This eventually resulted in the development of what is now called EBCT [electron beam computed tomography].

In 1984 Dr. Boyd and colleagues, working initially under the aspics of the University of San Francisco Physics Laboratory, developed a commercially viable electron beam scanner. A for-profit company, Imatron Inc., was developed, and then it was time to sell the scanners to academic institutions for cardiac research. It was initially called "ultrafast CT."

The design was radically different from conventional CT at the time. The idea behind ultrafast CT was a large bell-shaped X-ray tube. An electron beam [think back to the initial experiments of Röentgen] emitted from the cathode is focused into a narrow beam and then, by means of powerful electromagnets, deflected to impinge on a small focal spot on an annular tungsten target anode. The electron beam [and of course the focal spot] was electronically swept along at semicircular array along 210° of arc (Fig. 1.4). In order to perform a true cross-sectional image, the beam sweep must be at least 180° plus the width of the "fan beam," which for the Imatron scanner was 30°. To acquire rapid heart scans without table movement, ultrafast CT included four anodes and two detector arrays, each offset along the z-axis to acquire eight interleaved slices covering 8 cm of the heart. Although very fast speeds were possible, since there were no moving parts, as with then and current CT scanners, the limited tube current (650 mA) required slower speeds for acceptable mAs values and associated image quality. However, with ultrafast CT temporal resolution speeds of 50 msec and 100 msec, this was 10–20 times faster than possible at that time from conventional CT [and frankly would not be possible with mechanical CT until 20+ years later].

I started my cardiology fellowship in 1981 at the University of Iowa under the mentorship of the late Dr. Melvin Marcus. Dr. Marcus had already distinguished himself as a leader in the world of coronary physiology. The initial experiments were done in laboratory animals, but he longed to be able to study in detail human cardiac and coronary physiology. Recall this was a time early in the developments of nuclear perfusion imaging and the 30° and 60° "sector" two-dimensional echocardiograms. The only way to evaluate for the severity of coronary artery disease was direct invasive angiography.

Mel had published a paper showing that patients with severe aortic stenosis and severe left ventricular hypertrophy, but no evidence for obstructive coronary disease, evaluated in the operating room using a Doppler coronary flow meter placed directly on the coronary arteries, could result in decreased coronary artery flow reserve and angina related to the left ventricular hypertrophy [13]. If only he could study such phenomenon in adult patients outside of the operating room.

Dr. Marcus had heard of the potential for ultrafast CT to do noninvasive human "experiments" of cardiac structure, function, and flow. The University of Iowa agreed to purchase Imatron scanner #3, and I was sent to the UCSF Physics Laboratory, along with the late Dr. Andrew

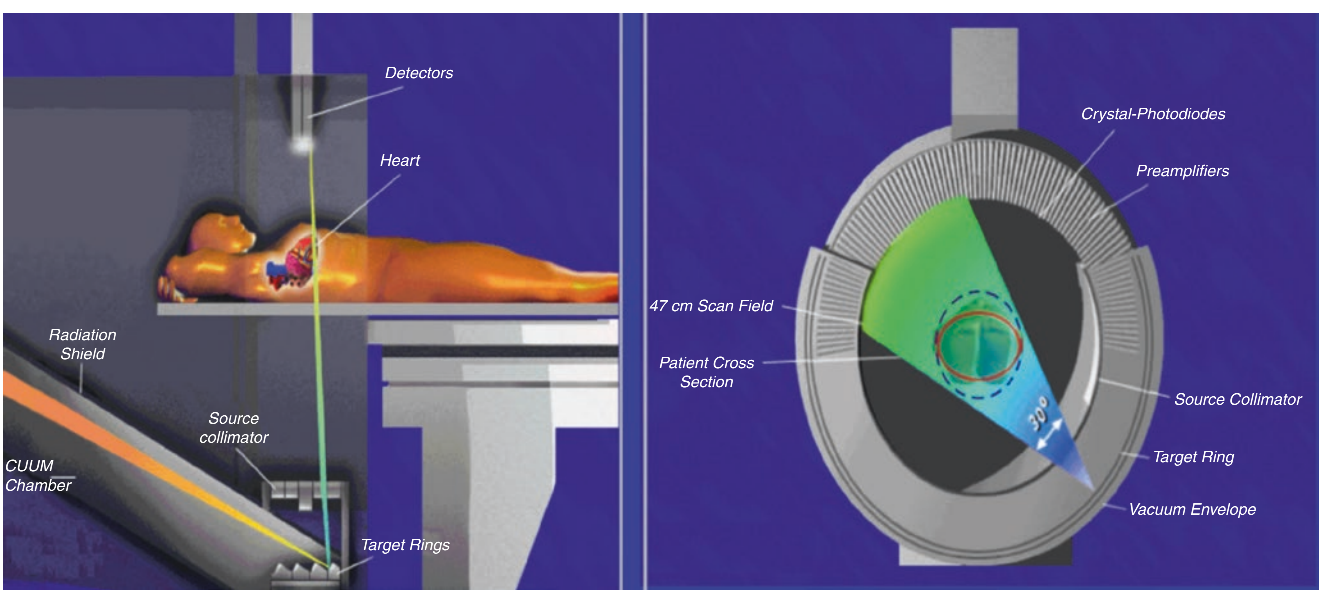

Fig. 1.4 Schematic of electron beam tomography. (Personal archives, John A. Rumberger, MD)

J. Feiring, to begin validation studies using ultrafast CT for two important parameters: accurate definition of global left ventricular muscle mass and regional myocardial perfusion.

During our time in South San Francisco, I got to know, learn from, admire, and befriend the "greats" in early cardiac CT including Dr. Bruce Brundage [cardiology], Dr. Charles Higgins [radiology], and Dr. Martin Lipton [radiology]. After many errors, trials, false endings, and misunderstandings of the physics of CT and image reconstructions, we were successful with our two primary objectives [14, 15].

Over the next 15 years, our laboratory at the University of Iowa and later at the Mayo Clinic, along with scores of other investigators all over the world, used ultrafast CT [later called simply electron beam CT (EBT/EBCT)] to validate a number of potential human clinical cardiac situations including quantitation of left ventricular regurgitant volumes [16], visualization of coronary artery bypass graft patency [17], segmental left ventricular systolic function [18], regional left ventricular diastolic function [19, 20], regional radius to wall thickness rations in normal volume overloaded left ventricle [21], right ventricular assessment in patients under consideration for lung transplantation [22], post-infarct left ventricular and right ventricular remodeling during the first year after myocardial infarction [23, 24], and revalidation of measurements of myocardial perfusion in animal models [25] and in humans [26].

Imatron, as a stand-alone provider of ultrafast CT, had many "suiters" during the years beginning with Picker International and later with Siemens. These associations later proved to be economically fatal.

Despite these and many other publications, imaging of the heart using CT was considered at the time as a "niche" and likely not to be applied widely in clinical medicine as magnetic resonance imaging and two-dimensional [and eventually three] echocardiography, both not involving exposure to ionizing radiation, gained more and more applications and notoriety. Ultrafast CT/EBT needed a "unique" application to clinical cardiology.

There had been reports as early as the 1960s using the presence of coronary artery calcification, detected at fluoroscopy, as a noninvasive definition of coronary atherosclerotic plaque. Early investigations at the University of Chicago showed a correlation with coronary obstructive disease and non-quantitation of coronary artery calcification using ultrafast CT [27]. However, it was the publication of a study from Mt. Sinai hospital by Agatston and Janowitz that set the course for the use of quantitated coronary artery calcium score [Agatston score] as a surrogate for clinical coronary artery atherosclerosis [28].

David King [as identified previously] was then the "scientific director" of Imatron and visited all US and foreign ultrafast CT installed sites to interest researchers in CAC [coronary artery calcification]. At the time, we had two installations of EBT at the Mayo Clinic, and we were imaging cardiac physiology [as noted above] and exploring applications of fast imaging of the respiratory system [cine angiographic imaging of patients with sleep apnea and exploring the application of ultrafast CT in detecting pulmonary emboli].

David tried to interest me in CAC in the early 1990s. I had four comments: (1) We know that CAC is associated with atherosclerosis, but it does not tell us the severity of coronary stenosis, (2) I am happy studying cardiac/coronary physiology that I know can be done with EBT, (3) I am not interested, and (4) find somebody else at Mayo that might find CAC valuable… *Should such comments strike me down as I stand.*

Dr. William Stanford and I edited the first book on *Ultrafast Cardiac CT* in 1992 [29]. At that time, we discussed the physics of CT imaging and had many of our colleagues submit chapters on their ultrafast CT research. One such chapter was from Drs. Agatston and Janowitz on the clinical applications of CAC scanning. I edited the chapter and felt that the "suggestions" for applications were a bit "imaginative," and I asked them to "tone it down" for the eventual publication.

I was aware peripherally of the research my colleagues Dr. Robert Schwartz in collaboration with a well-known cardiac pathologist, Dr. William Edwards, in looking at CAC in autopsy hearts using EBT. At the same time, epidemiologists from the University of Michigan, Drs. Pat Peyser and Lawrence Bielak, were conducting studies in the "Rochester Family Heart Study" looking at CAC in residents of Olmsted County, MN., in relationship to coronary angiography [30].

At the Mayo Clinic, we required all our internal medicine residents to participate in at least one research project during their residency. Dr. Brent Simons, who had been involved with Drs. Schwartz and Edwards in the pathologic studies of CAC versus coronary plaque studies, came to me to discuss his data and how to best analyze the information. He basically had a listing of CAC area measurements using EBT made at 3 mm intervals from the ostium of the autopsy coronary arteries and representative coronary histologic atherosclerotic plaque areas from the same coronary segments. I was not his academic advisor but suggested we start with a simple linear correlation of CAC areas versus histologic plaque areas. At the time the best program was called "Lotus 123." I took the data and displayed the information. What I saw was astounding and provocative: there was a clear, albeit scattered, linear correlation between CAC area and comparable atherosclerotic plaque area. I turned to Brent and said, quite literally: "Where the hell did you get these data?"