Coronary arteriography — it took a long time!

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CORONARY ARTERY DISEASE, with its potential sequelae of angina pectoris and myocardial infarction, is the most common form of acquired heart disease in developed countries. Before the 20th century much was known about the anatomy and pathology of the heart but the pathophysiology of ischemic heart disease was poorly understood.1,2 This essay will describe the development of techniques to visualize the coronary arteries with radiopaque substances and roentgenography. Factors that contributed to the time lag of more than half a century between the discovery of x-rays and the development of procedures to adequately and safely visualize the coronary arteries in humans will be reviewed.

The anatomy of the coronary arteries has been the subject of active investigation for more than three centuries.3 Accurate depictions of the epicardial coronary arteries are present in the works of Leonardo da Vinci and Andreas Vesalius. The smaller intramural branches of the coronary arteries were difficult to demonstrate by simple dissection, however. The development of postmortem injection techniques facilitated the study of the anatomy of the human vascular tree, including the coronary circulation.4 Richard Lower was one of the earliest physician-scientists to use injection techniques to study the coronary arteries. He observed in 1669 that the coronary arteries "come together again, and here and there communicate by anastomoses. As the result fluid injected into one of them spreads at one and the same time through both. There is everywhere an equally great need of vital heat and nourishment, so deficiency of these is very fully guarded against by such anastomosis."5 Julius Cohnheim, an influential German pathologist, concluded in 1881 that the coronary arteries were "end-arteries" and that any anastomoses were functionally insignificant. Although this view predominated for a generation, occasional European and American workers attempted to disprove Cohnheim's conclusion.6 The question of the existence and functional significance of coronary anastomoses would soon serve as a stimulus to investigators to combine postmortem vascular injection techniques with roentgenography.

With the discovery of x-rays in December 1895 by William Röntgen, a new approach to the study of cardiac anatomy became possible.7 X-ray equipment was introduced into laboratories in colleges and medical schools throughout North America with extraordinary speed. Less than three months after Röntgen's discovery, individuals in nearly fifty American institutions were experimenting with x-rays.8 In October 1896 Francis Williams, a pioneering American radiologist at Boston City Hospital, published his observations on the use of the fluoroscope in evaluating the cardiac silhouette.9 Within a month after the publication of Röntgen's original paper, two European physicians published a roentgenogram demonstrating the arterial supply of the hand obtained by injecting a radiopaque substance into the brachial artery of a cadaver.10 In one of the earliest American monographs on x-rays, William Morton, a New York physician, claimed, "In teaching the anatomy of the blood vessels the x-ray opens out a new and feasible method. The arteries and veins of dead bodies may be injected with a substance opaque to the x-ray, and thus their distribution may be more accurately followed than by any possible dissection." Elsewhere in this volume he observed, "One can hardly fail to be impressed with the wonderful results already achieved in this most attractive field of investigation as well as the enormous possibilities lying dormant in Prof. Röntgen's discovery... We can confidently look forward to more definite results and knowledge in the near future."11

European, British, and American workers published roentgenograms of the vascular systems of injected cadavers before 1900. Reflecting the popularity of stereoscopic images in this era, the German physician

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Vol. 70, No. 5, November 1984
Heinrich Hildebrand published a stereoscopic atlas of roentgenograms of the human arterial system in 1901. This atlas did not include the coronary circulation, however. The initial employment of x-rays and radiopaque substances in cadaver hearts to study the coronary circulation was stimulated in part by the unresolved issue of the functional significance of coronary anastomoses. In 1899 Walter Baumgarten of the Harvard Medical School published an extensive review on myocardial infarction in which he claimed, ‘‘The question of anastomosis receives considerable light from the method of examination with the Roentgen rays, which obviates the disturbance and destruction of small vessels which must occur in dissections or corruptions.’’ Baumgarten’s experiments with radiopaque substances in the coronary arteries were carried out in cats and dogs. Similar studies were undertaken by the German physicians Friedrich Jamin and Hermann Merkel, who published the first roentgenographic atlas of the human coronary arteries in 1907. In this publication, elegantly illustrated with stereoscopic roentgenograms, the authors presented their study of 29 hearts in which the coronary arteries were injected with a suspension of red lead in gelatin (figure 1). Coronary anastomoses were demonstrated in several of their injected specimens as were coronary occlusions.

James B. Herrick’s 1912 paper, ‘‘Certain Clinical Features of Sudden Obstruction of the Coronary Arteries,’’ represented a major advance in our understanding of the pathophysiology of coronary artery disease, angina pectoris, and myocardial infarction. Basing his conclusions on anatomic, pathologic, and clinical observations, Herrick refuted Cohnheim’s premise that the coronary arteries were strictly end-arteries. Among the evidence Herrick cited were the roentgenographic studies of Jamin and Merkel. Herrick also proposed

The clinical manifestations of coronary obstruction will evidently vary greatly, depending on the size, location and number of vessels occluded. The symptoms and end-results must also be influenced by blood-pressure, by the condition of the myocardium not immediately affected by the obstruction, and by the ability of the remaining vessels properly to carry on their work, as determined by their health and disease. No simple picture of the condition can, therefore, be drawn.

Although Herrick presented his paper before the prestigious Association of American Physicians and published it in the widely read Journal of the American Medical Association, the significance of his observations was not immediately appreciated. Writing a quarter of a century later Herrick explained

The fate of that early paper was a surprise to me and a keen disappointment. I did not realize, as I do now, that in medical history, as in the history of the growth of ideas in general, while some new facts are accepted as soon as announced, or at least attract enough attention to be subjects for discussion, very often others are passed unnoticed or unapproved until again brought forward in more striking form or with more convincing proof and at a time when the medical world is more ready to listen.

Although Herrick was familiar with the roentgenographic techniques of visualizing the coronary arteries in cadavers and realized the physiologic significance of the location and severity of obstructions of the coronary arteries, he did not propose the extension of contrast roentgenography to the study of the coronary arteries in the living human.

Before angiography in the living human would be safe and practical, several developments were necessary. Among these was the requirement for a nontoxic radiopaque substance that could be safely injected into the vascular system in vivo. In 1910 Franck and Alwens reported injecting soluble mixtures of heavy metals into the blood vessels of experimental animals. Although in some instances satisfactory images of the peripheral and pulmonary vasculature were obtained, the animals uniformly succumbed to the toxic effects of the substances. The authors expressed the hope that nontoxic compounds would be developed making vascular radiology in humans possible. An important advance occurred in 1921 with the introduction of Lipiodol as a contrast agent by the French physicians Sicard and Forestier. This substance, a

**FIGURE 1.** An illustration from F. Jamin’s and H. Merkel’s stereoscopic atlas of the anatomy of the coronary arteries in man, published in 1907. This is a postmortem roentgenogram of the excised heart of a 20-year-old man who died of pneumonitis. The coronary arteries were injected with a mixture of red lead and gelatin.
40% solution of iodine in poppy oil, had been a popular remedy in France since its introduction in 1901. It had been injected into various human tissues for years and was known to be radiopaque. Sicard and Forestier injected Lipiodol into the epidural space of a man and found that it produced no adverse effects. A short time later they found that experimental animals tolerated the intravascular injection of this substance. They subsequently extended their experiments to humans and found that the injection of Lipiodol into the antecubital vein permitted roentgenographic visualization of the pulmonary circulation. Although this was accompanied by coughing, no other ill effects were observed. Americans made significant contributions to the development of clinical arteriography in the 1920s. Sodium iodid was introduced as a contrast agent for urography in 1918 and was first administered intravascularly by Osborne and colleagues at the Mayo Clinic in 1923. In their report these authors proposed the use of this substance for vascular radiology.

Practical concerns regarding the management of patients with peripheral vascular disease led Barney Brooks, then a surgeon at Washington University, to study the intra-arterial injection of sodium iodid. He concluded, "An exact knowledge of the site and extent of occlusion of the arteries of the extremity is of great value in the prognosis and treatment of diseases of the extremities due to deficient arterial blood supply." He also observed that this procedure had "in several instances, established the fact that conditions presumed to be due to arterial obstruction had other causes. Also, in cases of arterial obstruction it is possible to obtain valuable knowledge as to the site and extent of the collateral circulation." Today, the parallels between peripheral vascular disease and coronary artery disease in terms of the location and severity of obstructive lesions and the patient’s signs and symptoms are apparent. In the late 1920s, however, it seems that no one proposed extending the practice of vascular roentgenography to the coronary circulation.

The development of relatively safe compounds for angiographic studies in humans removed a major obstacle for the further development of these techniques. Angiography in the living patient became a standard procedure during the 1930s due in large part to the pioneering work of Egas Moniz and his Portuguese colleagues. As had been the case with Barney Brooks, Moniz was motivated to a significant degree by practical questions relating to patient management. Aggressive operative treatment of intracranial tumors had recently been pioneered by Harvey Cushing, the innovative American neurosurgeon. Moniz recognized the potential value of cerebral angiography as an aid to the diagnosis and management of intracranial tumors as well as circulatory disorders of the brain. His group subsequently extended their experiments on angiography to the extracranial vessels and emphasized the diagnostic value of aortography. Vascular roentgenography had therefore been proved safe and technically feasible by this Portuguese group. Intracardiac injection of contrast material in the human was first reported in 1931 by Carvalho of Moniz’ group. These experiments were made possible by the recent development of a technique for human right heart catheterization by the German physician Werner Forssmann.

While an intern, Forssmann became impressed with the uncertainty of cardiac diagnosis. He was aware of the experiments performed nearly a century earlier by the French physiologists Claude Bernard, Auguste Chauveau, and Étienne-Jules Marey in which flexible tubes were introduced into the vascular systems of experimental animals and passed into the heart to obtain samples of blood. The circumstances leading to the catheterization of his own heart in 1929 and the technique he used are graphically described in his autobiography. Forssmann soon extended his experiments to include the intracardiac injection of contrast material through a catheter placed in the right atrium. Forssmann’s contributions together with the development of nontoxic contrast materials and steady advances in x-ray equipment and technique set the stage for the development of cardiac angiography and subsequently coronary arteriography.

By 1931, therefore, techniques were available to place catheters within the heart and to inject nontoxic radiopaque contrast material into the central circulation in man. The following year Peter Rousthöi of Stockholm initiated a series of experiments designed to study roentgenographically the coronary circulation by means of contrast agents. Rousthöi coined the term "angiocardiology" and demonstrated the coronary circulation in rabbits by injecting thorium dioxide into the proximal aorta. He also showed that retrograde catheterization of the left ventricle through the aortic valve could be performed easily without damaging the aortic valve. Rousthöi concluded it would eventually be possible to roentgenographically image the coronary arteries in man by extending the techniques he described in his paper.

The research efforts of many European investigators were disrupted by the events leading to World War II. By the early 1940s a few individuals in the western hemisphere were extending the pioneering experiments of Forssmann and other Europeans. Castellanos
of Cuba and Robb and Steinberg of New York had developed methods of safely opacifying the four cardiac chambers and the great vessels in man.\textsuperscript{28} Although these workers measured certain physiologic parameters, the main theme of their research was anatomic rather than physiologic. To evaluate the physiology of the heart and lungs, André Courand and Dickinson Richards used the cardiac catheter to record intracardiac pressures, calculate cardiac output, and measure a number of other physiologic parameters.

During the next quarter century improvements in techniques of gaining access to the central circulation, in radiologic equipment, and in catheter design facilitated the efforts of innovative physicians who demonstrated the usefulness of cardiac catheterization and vascular angiography. Advances in cardiovascular surgery were a major stimulus for this research. More precise anatomic diagnosis of congenital and acquired heart disease was required before potentially dangerous operative intervention.\textsuperscript{29, 30} One of the practical improvements in catheterization that simplified the procedure and made it safer was the development of alternatives to transcutaneous aortic puncture to gain access to the central arterial circulation. Fariñas, a colleague of Castellanos, proposed a safer method of introducing a catheter into the aorta. Blind puncture of the abdominal aorta in the paravertebral region was abandoned in favor of blunt dissection of the femoral artery followed by puncture of the artery with a trochar through which a catheter was passed.\textsuperscript{31}

In 1945 Nathan Grossman, working with Louis Katz in Chicago, reported his experiments to “show that it is feasible to instill substances directly into the coronary circulation without opening the thoracic cage.”\textsuperscript{32} He inserted a ureteral catheter into the right common carotid artery, which had been exposed by dissection. The catheter tip had been bent to 35 degrees and was placed in the ascending aorta just above the aortic valve leaflets, where contrast medium was injected. No attempt was made to selectively catheterize the coronary arteries, however. The same year, Radner of Lund, Sweden, reported his experiments in which he combined and extended the techniques of Moniz, Dos Santos, Castelanos, Robb and Steinberg, and others in an attempt to roentgenographically image the coronary arteries in man. Through their efforts, he claimed, “The major part of the human circulatory system has thus been made available for intravital exploration. There still exists, however, an important part of the visceral vascular structure which lies outside the scope of the angiographic technique, namely, the coronary blood vessels.”\textsuperscript{33} Radner’s technique of injecting contrast material into the ascending aorta reached through sternal puncture resulted in only faint visualization of the proximal coronary arteries. Moreover, it was accompanied by significant complications caused by the transternal approach and injection technique he used.

Further developments in the 1940s included the production of catheters made of polyethylene, a recently synthesized polymer of ethylene, and refinements of techniques to gain access to the central circulation that reduced the risk associated with transthoracic approaches to aortography. Encouraged by recent developments in thoracic and vascular surgery and building on the experience of Grossman and Radner, James Helmsworth and his colleagues at Cincinnati performed experiments in dogs in an attempt to visualize the coronary arteries roentgenographically. After these experiments were successful, Helmsworth extended his studies to six human subjects in whom a polyethylene catheter was inserted into the brachial artery and passed retrograde to the ascending aorta. He then injected iodopyracet (Diodrast) into the proximal aorta. His technique, like that of other workers for another decade, did not include introduction of the catheter into the coronary ostia. This nonselective technique did permit occasional visualization of the proximal coronary arteries. Helmsworth presented his results at the 50th Annual Meeting of the American Roentgen Ray Society, where a dicussant, Harold Kotte, observed

Coronary angiography presents an intriguing problem. One cannot deny the importance of a method whereby narrowing or obstruction of the coronary arteries can be demonstrated. However, the technical difficulties of adequate filling and proper exposure may be hard to overcome. The danger of introducing a foreign, oxygen-free medium into a coronary circulation already seriously compromised by arteriosclerosis is probably great, and anginal pain, dangerous arrhythmias or sudden death are to be feared.\textsuperscript{34}

Working in Gunnar Jönsson’s radiology department in Stockholm, where thoracic aortography and angiocardiography had been performed for five years, Di Guglielmo and Guttadauro published a well-illustrated monograph on nonselective coronary arteriography in 1952. Their report was based on 328 examinations in 235 patients in whom aortography or angiocardiography was performed. In most instances the catheter was introduced through the radial artery and, as was the case with all earlier workers, the coronary arteries were visualized after injection of contrast material into the proximal ascending aorta rather than by selective injection into the coronary ostia. They concluded that “aortography should be considered the best method now available for studying the coronary arteries” and elsewhere observed, “In the light of our findings, and
especially in view of the fact that in none of our cases have any significant ill-effects been reported, we believe that coronary arteriography should also be employed diagnostically in coronary disease.\textsuperscript{35} Jönsson later recalled the stimulus given to his research in angiocardiography and aortography by his innovative surgical colleague Clarence Crafoord and claimed, ‘‘The aim has always been to fulfill the demands put forward by the thoracic surgeons.’’\textsuperscript{29}

Surgical approaches to the management of coronary artery disease were developed by Beck in the 1930s, Vineberg in the 1940s, and Murray in the 1950s.\textsuperscript{36} The most promising techniques appeared to be endarterectomy, which had proved successful in the management of occlusions of the aorta and its branches, and direct anastomosis of extracardiac vessels to the distal coronary circulation.\textsuperscript{37} In 1955 Cannon and coworkers at UCLA, reporting experiments with nonselective coronary arteriography, claimed, ‘‘It is our belief that certain cases of atherosclerotic obliterative coronary artery disease are amenable to treatment by endarterectomy. At present no reliable clinical methods are available that permit the precise localization of a coronary artery obstruction.’’\textsuperscript{38} They attempted, as had other workers, to maximize the amount of contrast material entering the coronary arteries during nonselective proximal aortic injections. Their technique utilized a balloon-tipped catheter (similar in design to the more recently developed Swan-Ganz catheter) with an end hole distal to the balloon, which would be inflated to nearly totally occlude the ascending aorta at the moment the contrast agent entered the proximal aorta. They concluded, ‘‘It is suggested that a modification of this method could be applied in human coronary obstructive disease with good diagnostic result and with a morbidity no more severe than that experienced in cerebral angiography.’’ During the 1950s a number of other procedures were attempted to improve visualization of the coronary arteries during proximal arteriography, including phasic injection during diastole and injections into the sinuses of Valsalva.

It was becoming increasingly apparent that the toxic effects of intravascular contrast agents were dose related. This led Odman of Jönsson’s group in Stockholm to propose selective angiographic examinations in 1956, which were aimed ‘‘at visualization of each branch of the aorta separately . . . ’’\textsuperscript{39} Odman combined many recent advances in catheter technology and catheterization technique in his experiments. He used catheters that were preformed with curves at the distal end to facilitate their introduction into a specific branch of the aorta. Moreover, he used the simplified technique of percutaneous catheter introduction developed by another Swede, Seldinger, three years earlier. In contrast to earlier techniques, Odman found his method to be free of complications and ‘‘strikingly easy to perform.’’ However, he made no mention of attempting to selectively catheterize the coronary arteries in his report.

Selective coronary arteriography had not yet been proposed. In fact, concerns regarding the possible adverse effects of selective catheterization of the coronary arteries were often raised. Hughes, Miller, and Kolff of the Cleveland Clinic performed a series of experiments in 1956 and 1957 based on the premise: ‘‘Improvements in coronary angiography are basic to further advances in diagnosis and treatment of diseased coronary arteries. Exact localization of coronary occlusions by roentgen study must become possible if restorative surgical techniques ever are to be utilized.’’\textsuperscript{40} These authors revealed that ‘‘aortic pressure recordings were used to help to determine the position of the catheter, as a safeguard against inserting the catheter into the coronary artery itself.’’ However, they did attempt to place the catheter tip near the coronary ostia to improve visualization of the coronary arteries.

Mason Sones, another member of the Cleveland Clinic staff who had participated in the earlier experiments of Kolff and Miller, would develop truly selective coronary arteriography in the late 1950s. While performing aortographic examinations in patients with rheumatic valvular disease, Sones discovered that some injections would preferentially fill one coronary artery and that this caused no apparent harm to the patient. Sones presented his initial experience with semiselective coronary arteriography at the 32nd Scientific Session of the American Heart Association in Philadelphia in October 1959. After his studies of semiselective coronary arteriography (purposely directing the contrast into one of the sinuses of Valsalva), Sones had begun to perform true selective coronary arteriography in 1958. In April 1959 Sones obtained a special catheter from the United States Catheter and Instrument Co., which was ‘‘designed to permit direct catheterization of the human coronary orifices.’’\textsuperscript{41} Writing in 1960 he claimed, ‘‘Cine-coronary-arteriography is at the present time in an embryonic stage of development as a diagnostic method.’’\textsuperscript{42} Sones combined anatomic and physiologic considerations in developing his method of selective coronary arteriography. A preformed catheter with a tapered tip permitted selective entry into the coronary ostia but avoided complete obstruction of the coronary artery,
an event much feared by earlier workers who were not using tapered catheters. Furthermore, Sones used constant pressure monitoring combined with fluoroscopy to alert the operator to inadvertent complete obstruction of the coronary artery.

Sones' technique of selective coronary arteriography received wide publicity in July 1962, when it was published in *Modern Concepts of Cardiovascular Disease*. This brief paper included a concise description of the technique, a thoughtful discussion of the indications for the procedure, and a summary of complications observed in Sones' series of more than 1000 patients. It is of interest that Sones differentiated "segmental narrowing due to functional coronary artery construction . . . from fixed organic obstructions by repeated visualization before and after the use of amyl nitrite or nitroglycerin."41

Sones' development of selective coronary arteriography and the increasing interest among surgeons in operative approaches to the treatment of coronary artery disease signaled a period of rapid growth in coronary arteriography in the mid 1960s. Writing in 1961, Dotter and Frische had observed, "Considering the importance of coronary disease, it is surprising to discover that of the countless thousands of scientific articles published during the last quarter century little more than three dozen . . . deal with man's attempts to visualize the coronary arteries during life."42 The January 1963 issue of *Circulation* included a symposium on coronary arteriography.44 In the introduction to this symposium, Richard Greenspan noted the increasing frequency with which coronary arteriography was being performed in major medical centers. Although the authors emphasized that the technique was still primarily investigational, they did anticipate its more widespread application as experience was gained and medical and surgical approaches to the management of coronary artery disease evolved. A major impetus for widespread application of selective coronary arteriography came with the development of direct myocardial revascularization. This technique was pioneered at the Cleveland Clinic by Favaloro and colleagues with the encouragement of Sones.45

Many factors contributed to the development of selective coronary arteriography. Obviously, the discovery of x-rays by Wilhelm Röntgen in 1895 represented the essential scientific advance necessary for the eventual development of coronary arteriography. The demonstration of the feasibility of vascular catheterization in man by Forssmann, and the extension and refinement of this technique by others, was another critical development. Improvements in physiologic monitoring and imaging techniques and the development of cineangiography, which made possible the preservation of angiographic records, were all required. Other necessary advances were the manufacture of materials suitable for the construction of flexible and moldable catheters and the synthesis of nontoxic radiopaque substances. Once these and many other developments had occurred to make human angiography feasible, the major stimulus for the refinement and widespread application of these techniques was the growing possibility of surgical management of congenital and acquired heart disease. This was particularly true after techniques for direct myocardial revascularization were developed.

I thank Dieter Voss, M.D., for his assistance in translating several German articles that were reviewed during the preparation of this article.

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_Circulation_. 1984;70:781-787
doi: 10.1161/01.CIR.70.5.781

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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