Clinical Pathologic Correlations in Coronary Artery Disease

The extensive clinical utilization of coronary angiography and coronary artery surgery in recent years has heightened interest in the anatomy and pathology of the coronary arterial tree. Much new information has indeed been amassed concerning the patterns of distribution of the coronary arteries, the size and extent of interarterial coronary anastomoses, the nature, location, and extent of coronary artery narrowing and occlusion, and the correlation of these findings with pathologic changes in the myocardium and with clinical manifestations of coronary heart disease. Many years ago these matters were the subjects of extensive clinicopathologic studies based on the postmortem injection-plus-dissection technic developed by Schlesinger. We are, therefore, interested here in reviewing these early findings as well as the recent observations and assessing their significance for the many difficult problems that arise in the clinical management of coronary artery disease today.

Anastomoses

The most effective protection against the otherwise dire effects of coronary occlusions is afforded by the interarterial collateral circulation of the heart. In 1669 Lower described the development of anastomoses following arterial occlusion, but he did not state whether he had observed interarterial anastomoses in the coronary arteries of the normal heart. In a prolonged controversy, anatomists have maintained that interarterial coronary connections are normally present in man. Since aqueous solutions injected into one coronary artery appear immediately in the others, they are evidently connected at least by arteriolar and capillary vessels. Physiologists, however, have insisted that functionally the coronary arteries are end arteries inasmuch as acute experimental ligation or clinical occlusion of a large artery always produces myocardial infarction. Anastomoses present in the normal heart, therefore, are not of sufficient size and number to be functionally significant since they do not prevent myocardial infarction.

The development of larger, functionally important interarterial anastomoses has been demonstrated repeatedly following gradual experimental or atherosclerotic occlusion of a coronary artery. These collateral channels between coronary arteries serve to nourish myocardium beyond complete occlusions that would otherwise undergo necrosis, and they also serve as bypasses or detours to connect proximal and distal portions of occluded arteries. It has been shown experimentally that dogs and pigs may survive gradual complete occlusion of one or more main coronary arteries with little myocardial damage. The clinical counterpart of these experiments, i.e., the occasional complete absence of clinical symptoms and of myocardial infarction or fibrosis despite multiple, old coronary artery occlusions, emphasizes the functional significance of the compensatory collateral vessels.

The hearts of patients with angina pectoris usually show one or more occlusions of the coronary arteries, a rich collateral development, and variable myocardial fibrosis or infarction. While there is a general relationship between the incidence of coronary occlusion and the occurrence of angina

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pectoris, other modifying factors, such as the precise location of occlusions, the importance of the vessels involved, the adequacy of the collateral circulation, the rates at which occlusions or narrowing develop, the activity, psychological and physical condition of the patient, such as anemia or thyroid function, and the temporary influence of emotion and of vasomotor reflexes, are also of great importance. Although damage to the heart may be reduced by the development of the collateral circulation, the margin of safety, or, as it may be termed, "the coronary reserve," is lessened.

By the Schlesinger lead-agar or barium-gelatin injection technic the functionally important collateral channels were found to be generally more than 40 μ in diameter in fixed sections, which correspond to 80 μ in fresh tissue. These large anastomoses were ordinarily absent in normal human hearts, but were demonstrated in hearts with hypertrophy, coronary arterial narrowing or occlusion, and in hearts of patients with anemia. Several postmortem injection studies done with varying materials and technics, have presented conflicting evidence concerning the size of interarterial coronary anastomoses in normal human hearts. Some investigators have concluded that large functionally significant anastomoses are normally present. Pitt, on the other hand, and the many recent clinical angiographic studies have confirmed Schlesinger's initial conclusions. Although angiographic dyes are water soluble, they are usually visible by X-ray only in the arterial branches larger than 100 μ in diameter mainly because of the limits of radiographic resolution. These intercoronary anastomoses are not visualized in normal human hearts, but do appear in the presence of cardiac pathology and therefore provide information of great functional and clinical significance. It is of interest that both the earlier studies by the Schlesinger technic and the more recent angiographic studies visualize the collateral channels by X-ray.

Parallel to these anatomic observations, many physiologic studies have amplified and confirmed the protective significance of intercoronary anastomoses disclosed by the morphologic injection technics.

The general older view of coronary arteriosclerotic heart disease as simple progressive myocardial damage with narrowing and occlusion therefore is not tenable. Instead, the final condition of the myocardium is the resultant of opposing anatomic and physiologic factors, i.e. the opposing morphologic processes of atherosclerotic obstruction versus the compensatory development of large collateral channels and also variations in blood supply and demand.

The time required for the development of functionally significant anastomoses has been studied in animals. Available evidence indicates that although sizable interarterial anastomoses become visible within days after sudden coronary occlusion, several weeks are necessary for their rich development, and several months may elapse before their full potentiality is realized. A pressure gradient between occluded and nonoccluded arterial segments and hypoxia are important factors in the development of these collateral vessels. The slow development of these channels as well as of the inflammatory reaction to necrosis emphasizes the importance of rest and reduced activity for many weeks after acute myocardial infarction, contrary to the current tendency to early ambulation. Similar efforts to reduce the cardiac requirement for blood would seemingly apply to patients before infarction develops, when angina pectoris first appears, or when the frequency or intensity of the attacks suddenly increases. Such changes in cardiac pain signal a new imbalance in blood supply and demand in the heart. Ample evidence exists that reduced cardiac work favors healing of the infarct, reduces the extent of myocardial damage, lessens liability of rupture, and provides time for the development of these anastomotic channels. The slow development of a richer anastomotic circulation is also apparently responsible for the occasional clinical improvement of patients with angina pectoris, the collateral channels acting to offset the narrowing or occlusion.

Coronary Angiographic Studies

Studies in living patients have confirmed many earlier anatomic and experimental observations and have extended our knowledge of the coronary circulation. The angiographic group differs from the old postmortem series in that it represents an earlier stage of the disease compatible with survival. In general, the postmortem findings are anatomically more reliable, but give, however, only inferential insight into functional blood flow. In many comparative analyses the angiographic evidence of coronary narrowing and occlusion conforms closely to the anatomic findings. The almost invariable appearance of collateral channels when stenosis is marked is verified by angiography. It is stated, indeed, that "the presence of a collateral..."
circulation is helpful in defining the degree of stenosis. In addition, it will aid in predicting the results of revascularization procedures.\textsuperscript{19} A rapid runoff of the injected material indicates a rich collateral network that may be valuable in bypass surgery. Similarly, areas of infarction devoid of blood supply can be identified, thereby forestalling vain attempts to improve blood supply to the region.

A number of technics have been used for the measurement of myocardial blood flow during selective coronary arteriography. Indocyanine, krypton, xenon, and other substances have been used. The accuracy and usefulness of these methods are still under study.

**Hazards of Coronary Arteriography**

Coronary arteriography is not devoid of risk.\textsuperscript{18, 20} Transient episodes of cardiac arrhythmias, acute cardiac ischemia, acute pulmonary edema, vascular hemorrhage at the site of puncture, vascular thrombosis, damage to the coronary arteries by the catheter, focal myocardial necrosis, and cardiac perforation are among the complications. Untoward incidents occur in 1–7% of patients, depending on the technic employed and the experience of the group.\textsuperscript{21} In a series of 900 cases significant, but nonlethal complications occurred in 2.2%.\textsuperscript{22–25} In experienced hands a mortality of approximately 0.1% may be achieved.\textsuperscript{26} Mortality rates above 0.3% are considered unacceptable.\textsuperscript{27}

Experienced personnel, careful monitoring of cardiac rhythm, and adequate facilities for immediate resuscitation and external stimulation and countershock are mandatory.

**Indications for Coronary Arteriography**

Which patients should be advised to undergo the unavoidable mortality, morbidity, stress, and expense of this procedure? Angiography provides information necessary for surgical procedures such as bypass surgery in which the location of occlusions, of collateral blood flow runoff, and of myocardial damage are important considerations. Whether the operation itself is indicated may be decided by the angiographic findings. In patients with angina pectoris and aortic stenosis, it is important preoperatively to assess the relative significance of the valvular and coronary lesions.

The authors do not believe that coronary angiography should be undertaken merely to establish a diagnosis of angina pectoris, except under rare circumstances. The presence of arterial narrowing or occlusion does not establish a clinical diagnosis of angina pectoris. There is ample evidence that gradually developing occlusion of one or more arteries may occur without any cardiac symptoms. Conversely, some patients, particularly those with arterial hypertension, marked valvular disease, congenital heart disease, myocardial infarction, or pericarditis may have angina pectoris or cardiac pain mimicking angina pectoris, without coronary heart disease. Rarely a patient, such as an airplane pilot, or bus or truck driver, may be requested by employers to obtain angiographic clearance, but the wisdom of such a requirement may be debated.

It must be reiterated that the doctor-patient relationship has the welfare of the patient as its prime objective. Every ethical principle rejects the performance of angiography in man solely for the discovery of new knowledge unrelated to any therapeutic benefit to the patient.

**Surgical Relief of Coronary Occlusion**

The therapeutic problem in coronary artery disease is created by stenosis or complete occlusion of a vessel with consequent diminished coronary blood flow. To achieve direct relief of coronary disease by introducing a new source of arterial blood supply to the ischemic but viable myocardium, the following procedures have been performed in the past on man: (1) application of grafts of neighboring tissues (pectoral muscle, omentum, lung, stomach, jejunum); (2) production of pericardial adhesions; (3) myocardial insertion of an actively bleeding artery; (4) anastomosis of the coronary venous system with neighboring arteries; (5) ligation of internal mammary arteries; (6) endarterectomy; and (7) resection of atheromatous arterial segments with graft replacement. These procedures have been subjected to the test of animal experimentation, but, in addition, patients have undergone operations, and favorable effects on angina pectoris have been recorded. Despite many early enthusiastic reports, they have all now been generally discarded.

Currently, aortocoronary-vein bypass is being enthusiastically hailed as a major conquest, and some 20,000 operations evidently have been performed in the U.S.A. in the past 12 months.

The morphologic characteristics of coronary atherosclerosis are indeed favorable to surgical intervention. The obstructing lesions are in the main stems or primary branches, are mostly localized and segmental, are almost entirely epicardial, and 70% lie within 4 cm of the coronary
ostia. The preoperative angiographic portrayal of the sites of coronary obstruction, the appraisal of the collateral runoff, and the extraordinary advances in surgical technic and in medical management during and following operation favor success.

Information on which to evaluate the operation is as yet meager. Some of the urgent questions that must be answered before the procedure can be confidently advised to patients are as follows: Is survival of patients with angina pectoris increased? What is the incidence, degree, and duration of improvement? Are myocardial infarction and congestive failure prevented? Is myocardial function improved? What is the duration of patency of the vein grafts and the quantity of blood flow through them?

Fragmentary data indicate that in some series, after 1 year, 22% of vein grafts are occluded, 18% of patients have sustained a myocardial infarction, and cardiac function is worsened in 50% of those with previous myocardial damage. In another series in which 105 vein grafts were assessed angiographically, 20% were occluded 2 weeks postoperatively and 50% were occluded in 1 year. In a series of 450 patients, 11% had acute myocardial infarction within 30 days after operation. In some centers where the operative death rate is only 3%, operative mortality increases to 15% if the myocardium is severely damaged. The interpretation of lessened angina pectoris after surgery is also beset with many difficulties of interpretation. For example, the nerve pathways from the heart to the nerve roots are not clearly defined. They traverse a wide pathway and may be transected by the operative procedure with abolition of the pain, but without changing the coronary blood flow, or indeed affecting the heart in any way. It is noteworthy in this connection that 80–90% of patients report complete or partial relief of angina pectoris, but the objective assessment of the results of operation with exercise testing and study of left ventricular function suggests lesser degrees of improvement.

At the present time we believe that the only definite indication for bypass surgery is disabling angina pectoris unresponsive to medical treatment in patients without severe myocardial damage in whom the operative risk is commensurate with the anticipated improvement. The results in patients with refractory congestive failure have been unsatisfactory. The extension of bypass surgery to patients with acute coronary obstruction (cardiac pain) without infarction and to patients with infarction and continuing pain or hypotension should be considered at present as experimental. A somewhat more detailed discussion with which we are in agreement has been presented recently by C. K. Friedberg.

A central registry for data from the centers practicing these procedures is urgently needed. Controlled prospective studies comparing the results with randomized groups of similar patients managed without surgery are necessary.

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