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A Critical Review of Clinical Arteriogenesis Research

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In human hearts, an extensive pre-existing collateral network is present. This was shown unequivocally some 50 years ago in a series of very detailed post-mortem angiographic studies. In these studies, it was also observed that the pre-existent collateral vessels enlarge upon closure of an epicardial coronary artery, resulting in large collateral conduit arteries, in sharp contrast to earlier claims that human coronary arteries are functional end arteries. These insights still form the basis for the concept of arteriogenesis as positive remodeling of pre-existent arteriolar connections. Subsequent experimental studies disclosed the putative role of circulating cells, especially monocytes, which invade the proliferating vessel wall and secrete growth factors, degrading enzymes and survival factors that are required for the development of a mature collateral circulation. Experimental stimulation of arteriogenesis is feasible but to date a relatively low number of clinical studies, with no or limited success, have been performed. The use of intracoronary derived collateral flow index can increase the sensitivity to detect the effects of pharmacological compounds on arteriogenesis, which is important in first proof-of-principle studies. These invasive measurements also allow the detection of patients with an innate defect in their arteriogenic response to coronary obstruction. In a reversed bedside-to-bench approach, the characterization of ribonucleic acid and protein expression patterns in these patients generated new targets for therapeutic arteriogenesis. (J Am Coll Cardiol 2010;55:17–25) © 2010 by the American College of Cardiology Foundation

A little more than 50 years ago, the first of a large series of studies on the extent of the collateral circulation in the human heart was published (1). Using high-resolution post-mortem angiography, these studies delivered final proof of the presence of collateral vessels between the different vascular territories of the normal healthy human heart, refuting claims that coronary arteries are functional end arteries. These studies also showed that the diameter of these pre-existent collateral vessels increases upon coronary occlusion. This still forms the basis for the concept of arteriogenesis, which is the development of large caliber collateral arteries from a pre-existing network, in response to arterial occlusive disease.

Experimental studies showed that the increase in diameter of collateral vessels is not passive dilation, but active proliferation of endothelial as well as smooth muscle cells. This opened the field for pharmacological modulation of collateral vascular development.

Currently, several candidates for pharmacological stimulation of arteriogenesis are known, the tools to measure the effects in patients are available, and the first clinical studies have been published. The intracoronary measurements of collateral flow in combination with ribonucleic acid microarray techniques and proteomics now also allow the identification of biological pathways that are linked to insufficient collateral artery growth. This opens new ways to find arteriogenic targets in patients that subsequently can be tested in validated experimental models. The present review is dedicated to 5 decades of clinical arteriogenesis research, summarizes our current understanding of arteriogenesis from a historical perspective, and outlines future developments.

Morphology of the Coronary Collateral Circulation in Humans: Post-Mortem Analysis

Precise morphology remains the province of post-mortem angiography. Some 50 years ago, it was widely believed that the coronary arteries of humans were end arteries (2). However, when using a more precise technique of post-mortem angiography, it was convincingly demonstrated that, in fact, in all human hearts an extensive network is present, connecting the different vascular territories of the heart (3). The contrast medium employed in this technique consisted of bismuth oxychloride 20% in gelatin prepared from a filtered solution, resulting in a maximal particle size of 2.0 μm and penetration to a minimal lumen diameter of 15 μm. Another important aspect for maximal penetration is pressure control of the injection of the contrast medium and nonsimultaneous injection of the left and the right coronary arteries.

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Abbreviations and Acronyms

CFIp = pressure-derived collateral flow index

FGF = fibroblast growth factors

GM-CSF = granulocyte-macrophage colony-stimulating factor

LAD = left anterior descending artery

LCx = left circumflex artery

MCP = monocyte chemotactic protein

RCA = right coronary artery

Anatomy of pre-existing coronary anastomoses. In the normal heart, superficial and deep collateral arteries are present. Superficial collateral arteries are found mainly at the interface between arterial territories, located at the anterior wall of the right ventricle, between branches of the left anterior descending artery (LAD) and the right coronary artery (RCA), near the posterior interventricular groove between the RCA and the left circumflex artery (LCx) (varying greatly depending on the balance of RCA and LCx), near the apex between branches of the LAD and marginal branches of the RCA and LCx, and in the atrial wall. In contrast to the dog, in humans, superficial collateral arteries are relatively small in number and caliber (20 to 200 μm in the healthy human heart).

Deep collateral arteries are more frequent than the superficial collateral arteries and are often of larger caliber (100 to 300 μm, sometimes even more). Transventricular septal collateral arteries are well recognized, connecting the LAD and the posterior descending artery, arising from RCA or LCx. Transventricular collateral arteries are sometimes exploited to open chronic total coronary occlusions in a retrograde fashion (4). Collateral arteries in the subendocardial plexus of the left ventricle form a network of intercommunicating arterial channels throughout the free wall, largely conforming to the columnae carneae. They are rather poorly represented in clinical angiography, possibly on account of intermittent filling and dilution of contrast medium. A schematic overview of the anatomic location of collateral arteries in the heart is provided in Figure 1.

Enlargement of coronary collateral arteries in obstructive coronary artery disease. Evidence from morphological studies is entirely consistent with the concept that the larger caliber collateral arteries displayed in disease result from enlargement of pre-existing anastomoses of smaller caliber in the normal heart. There is no need to postulate new arterial anastomoses in the human heart. First, there are no anatomic patterns of enlarged collateral arteries in disease that do not have their counterparts in the normal heart. Second, there are sufficient numbers of anastomoses in the normal heart to account for the numbers found in disease. The difference is not in number but in size, showing a shift to the right regarding vessel diameter (5) (Fig. 2).

Ischemic myocardial damage and the collateral circulation. It has long been observed that the extent of ischemic myocardial damage consequent on coronary artery occlusion usually falls short of the entire arterial territory. The background in human coronary disease is extremely heterogeneous with many factors involved, but the outstanding factor that limits the extent of myocardial damage following complete coronary occlusion is the degree of development of the collateral circulation at the time (6). Where there is only a small increase in diameter of collateral arteries, damage tends to be massive. Moderate enlargement greatly restricts the extent of the damage. Where the subendocardial plexus has

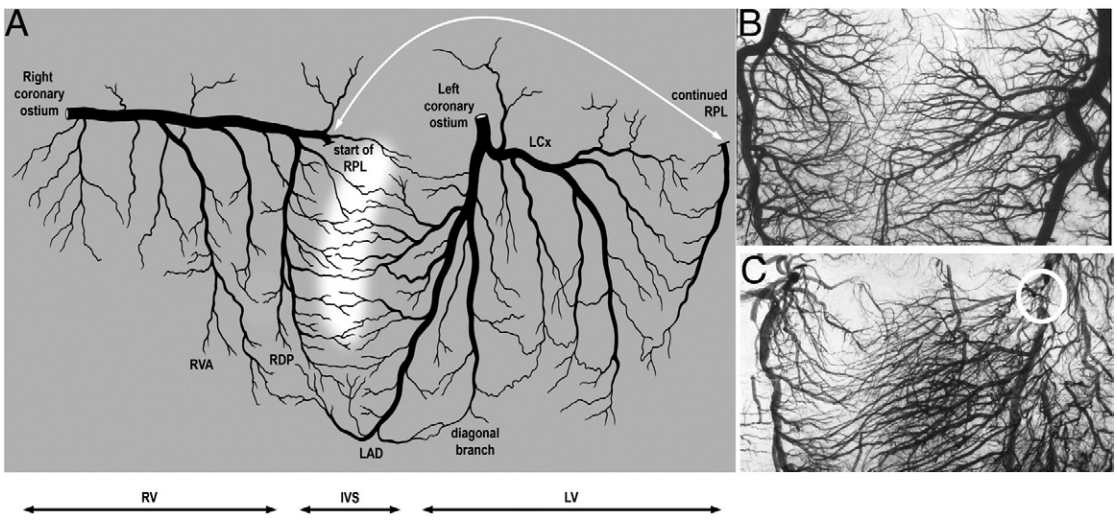

Figure 1 Coronary Collateral Circulation

(A) Anatomic distribution of pre-existing collateral vessels in the heart. The interventricular septum (IVS) **(highlighted area)** is of special interest, showing a large amount of collateral vessels. **(B)** Post-mortem angiogram showing pre-existing collateral vessels in absence of coronary artery disease. **(C)** Outgrowth of collateral vessels in presence of obstruction of the left anterior descending artery (LAD) **(white circle).** LCx = left circumflex artery; LV = left ventricle; RDP = posterior descending artery; RPL = right posterolateral artery; RV = right ventricle; RVA = right ventricular artery.