Arterial-venous relationships in the human left ventricular myocardium: anatomic basis for countercurrent regulation of blood flow

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ABSTRACT The mechanism by which myocardial blood flow varies in response to metabolic demand is obscure. One hypothesis is a countercurrent regulation of arterial caliber by diffusible substances carried in venous blood. To study the anatomic basis for blood flow regulation, we performed combined arterial and venous injections in 20 human hearts and studied left ventricular intramyocardial vessels with radiography, 100 μm thick sections, and reconstructions of serial histologic sections. Penetrating arteries lie in interstitial spaces and are closely related to accompanying veins. These interstitial veins partially surround and are indented by branch arteries. A second system of veins lies within muscle fascicles between interstitial spaces and is not related to arteries. The isolated veins have collateral connections with interstitial veins and join them in the subepicardium. This vascular anatomy could allow arterial caliber to be regulated by diffusible substances carried in the interstitial veins. Arterial dilatation might prolong this effect by partial obstruction of interstitial veins, with the isolated venous system providing an alternative pathway for venous drainage and washout. The study shows that a vascular arrangement is present in human left ventricular myocardium that could provide a countercurrent regulation of blood flow with diffusible substances carried in venous blood. Circulation 74, No. 6, 1195-1202, 1986

THE MECHANISM by which the regional flow of blood in the myocardium is controlled is unclear.1-5 Various neural, humoral, and vascular mechanisms have been proposed. We considered the possibility suggested by others,6-10 on the basis of experimental studies, that a countercurrent regulation of arterial blood flow by diffusible substances carried in venous blood may exist. However, little information is available on the anatomy of arterial and venous relationships in human ventricular myocardium.

The majority of work on the anatomy of coronary vasculature has been on the arterial side of the circulation.11-18 The basic architecture of the distribution and branching patterns, relationships of capillary beds, and size relationships of the arteries within the myocardium have been determined. Most studies on the coronary arterial vasculature within the left ventricular free wall are in agreement on the following observations. Epicardial vessels begin to branch within the epicardium and send tributaries into the myocardium at right angles to the main vessels. These branches, which range in size from approximately 400 to 1500 μm, subdivide in turn into a treelike pattern. Two types of arterial patterns have been described in the myocardium. One is a “branching” type, which, after entering the myocardium, quickly divides into a fine network that supplies the outer three-quarters of the myocardium. The other is a “straight” type with arteries of approximately 500 μm, which divide less frequently than the “branching” type and reach the endocardium with little or no reduction in size. The “straight” type of arterial pattern supplies blood to the subendocardial myocardium, and occasionally it has been observed that these vessels will enlarge upon reaching the endocardium, due to confluence of tributaries. When anastomoses exist between different coronary arteries, they have been observed in the subendocardial areas. Capillary beds exist throughout the ventricular wall. The largest beds are located subepicardially and subendocardially.

Considerably less work has been done on the intra-
mural venous system, although it seems generally agreed that there are at least twice as many veins as arteries in the heart wall. Kadar studied the relationship between coronary arterial and venous circulation by plastic corrosion casts of hearts of both animals and humans. His studies revealed a parallel arrangement between arteries and veins, in which arteries were usually accompanied by two veins and the vessels traveled together within the myocardium. This relationship was most evident in the dog and less so in man and other mammals. Kadar suggested that arterial pulsation assisted venous drainage. Kiss also studied arterial venous relationships and reported results similar to those of Kadar. In addition, he noted that the arteries and veins were encapsulated by a sheath of tissue. He felt that tension exerted on the vessels from the sheath aids in coronary blood flow regulation. Most studies have been restricted to either the arterial or venous aspect of the coronary anatomy. The purpose of this study was to investigate the interrelationships between the intramural arteries and veins by angiography, serial sectioning, and graphic microconstruction.

Materials and methods

Hearts from 20 patients with no clinical suspicion or gross evidence of cardiac disease were removed at autopsy and the coronary arteries were injected with a barium-gelatin-pigment mass at 100 to 150 mm Hg pressure. To obtain filling of the venous system, cannulas were placed in the coronary sinus and posterior descending vein, and the venous injection was carried out either before, simultaneous with, or after the arterial injection. Yellow injection mass was put in the arteries and green injection mass in the veins. The order of injection had no clear effect on the completeness of filling, which varied considerably from region to region and between hearts. After injection, the heart was immersed in 3.7% formaldehyde solution and fixed in distension at 30 to 40 cm H2O pressure by intracavitary formaldehyde solution introduced through cannulas in the atria and great arteries. After fixation, stereoscopic radiographs were prepared of the intact heart and the transverse slices into which it was cut.

Transverse regions of ventricular myocardium were removed from hearts with satisfactory filling of intramyocardial arteries and veins. A section was embedded in gelatin, with a mounting block placed on top of the section. Gauze was placed over the whole preparation and, after the gelatin became firm, the tissue section and mounting block unit were placed in the freezer for 24 hr. Immediately after removal from the freezer, the tissue was sectioned with a sliding microtome at 200 μm intervals. Sections were placed in transparent sleeves with glycerin holding solution and sealed. The coronary vasculature was examined under a dissecting microscope.

Transmural specimens of left ventricle with good injection were routinely processed and embedded in paraffin. Before sectioning, reference marks were made in the blocks by slitting edges on each side of the block with a razor blade and injecting India ink with a needle to make a black dot on the final tissue section. The paraffin blocks were then serially sectioned at 8 μm, and sections stained with hematoxylin and eosin. This method was chosen to preserve the relationships of the myocardium and a distended vasculature with different colored masses injected in arteries and veins. In our experience, plastic injections, which require destruction of the surrounding tissues, and Microfil injections, which have severe shrinkage artifact after tissue processing and penetrate the entire vascular bed, are less suitable for this type of study.

A microprojector was used to display the image of the histologic section on the working surface of the table. The magnification of the slides was adjusted for the resolution of the vessels and the sections were traced, transferring registration marks, arteries, veins, interstitial spaces, and cardiac muscle bundles by color coding. The tracings were checked with the slides for accuracy. A standard method of graphic projection and microreconstruction drawing was used to obtain the final images.

Results

Gross examination of the 20 hearts and study of the stereoscopic radiographs showed normal anatomic patterns of major epicardial coronary vasculature. It was also evident that the branches of the epicardial vessels were present in the left ventricular wall at right angles to the vessels on the surface. The extent of injection was determined and a decision as to whether the heart should be used for further study was made. The stereoradiographs rendered good detail of the arterial vascular tree, but the pattern of the smaller intramural arteries was obscured because of the density of the injection mass.

A closer examination of the left ventricular wall and its vasculature was obtained through study of the serial 200 μm sections. The color differential of the injection medium was an aid to observation. General branching patterns and distribution of arteries and veins were seen under the dissecting microscope, but no specific conclusions could be drawn. Approximately twice as many veins as arteries were observed and some of these vessels could be seen to intertwine about each other. The observations indicated that specimens needed to be chosen for histologic serial sectioning and graphic microreconstruction to allow adequate visualization of the interrelationships of the intramural arteries and veins.

The microreconstruction in figure 1 is shown in the left posterior oblique position. The drawing is a lateral projection of coronary arteries and veins and the interstitial space within which they course. The vessels are reconstructed from epicardium to endocardium. Only one interstitial space among those followed completely to the endocardium was depicted because of the complexity of the vascular contents. The microreconstruction shows that the epicardial vessels begin to divide within the epicardium. Interstitial spaces form around these vessels soon after they enter the myocardium. The muscle fibers are oriented in the same direction as the longitudinal axis of the interstitial spaces. As the
vessels course through the myocardium, they are continually dividing and branching. At the same time the interstitial spaces, which start subepicardially as large spaces, divide to accommodate the increasing number of branches. Histologic sections (diagrammed in figure 2) demonstrate the close relationship of arteries to veins seen in the microreconstruction. The vessels spiral about each other as they course from epicardium to endocardium. At some stages the relationship is so intimate that the artery is almost completely enveloped by the vein.

The interstitial spaces within which these vessels run rotate almost 180 degrees from their origin in the subepicardium to their termination at the endocardium. Some interstitial spaces contain both arteries and veins, while others contain only veins. The ratio of the total number of vessels in any one section is approximately two times as many veins as arteries. In general, the diameter of the vessels decrease in size from the epicardium to the endocardium, and there is a parallel decrease in the size of the interstitial spaces. About halfway through the myocardium, most vessels are individually surrounded by their own interstitial space. In some cases the arteries seemed to increase in size in the endocardium, apparently due to a confluence of tributaries.

It seemed from these first microreconstructions that there were two classes of veins. Some veins were related to arteries and some were independent of arteries. To further understand this arrangement, a microreconstruction was done of representative interstitial areas. Figure 3 is a microreconstruction drawing of three interstitial spaces. The front (1) and back (3) spaces contain both arteries and veins, whereas the central (2) space contains only a large venous component. Note that the venous components of the front and back spaces are connected with the central venous channel (figures 3 and 4, C and D). This was a typical anatomic pattern among the venous channels of the heart. Although the central venous channel has numerous small vascular connections with the veins in the front and back interstitial areas, these small venous connections evident in the photomicrographs of figure 4 were omitted from figure 3. After receiving venous connections from the front and back interstitial areas, the central venous channel returns blood to the epicardium (see arrow figure 3).

Both figures 1 and 3 demonstrate a close relationship of arteries and veins. The next objective was to reconstruct this relationship in more detail. Figure 5 is an enlargement of an area that was eliminated from the microreconstruction in figure 3. Note the arterial branch coming off the artery in the front interstitium (figure 3, box), which is the beginning of the arteriole that was reconstructed in figure 5. In this microreconstruction, as in the photomicrograph in figure 6, B, the

**FIGURE 1.** Microreconstruction of coronary vessels in the human left ventricle viewed in the left posterior oblique position. The large vertical vessels are in the epicardium, and the horizontal branches in the myocardium. Veins appear darker than arteries. The transparent interstitial space encapsulates the vessels.
FIGURE 2. Diagrammatic representation of the rotation of the interstitial space. The arrow in the central diagram corresponds to the spatial rotation within the block. A through E are approximate locations of the histologic sections shown below. The upper image is a representation of interstitial rotation.

FIGURE 3. Microreconstruction of the contents of three interstitial spaces with an alternative venous pathway. Veins appear darker than arteries. At A there is confluence of veins from spaces 1 and 3 with the alternative venous pathway. Arrows A through D correspond to the photomicrographs in figure 4. The small box that surrounds the arteriole is reconstructed and enlarged in figure 5.
FIGURE 4. Photomicrographs of the interstitial areas 1, 2, and 3, shown in figure 3. A to D correspond to the levels of sections A to D in figure 3. At levels A and B there are no major venous connections between spaces 1 or 3 and 2; the connections do occur in C and D.
artery is almost completely enveloped by the vein. The microreconstruction drawing also reveals an unconventional anatomic pattern of veins. The vein begins as a large vessel, then breaks up, only to have the branches rejoin, forming a large vessel. Along this course of venous division, note that the arteriole intertwines through the spaces between these veins. The arteriole gives off many branches in the intervening spaces. Some branches follow recurrent, anterior, and posterior paths about the vein, continuing into the surrounding tissue (figures 5 and 6, A).

**Discussion**

A number of factors have been identified that can affect coronary blood flow, including physical, myogenic, and metabolic factors. Feigl has written an excellent review of this subject. The physical factors that regulate blood flow are effective perfusion pressure and extravascular pressure. The coronary vascular resistance changes in a linear fashion with the perfusion pressure, thereby maintaining a constant flow of blood in the heart wall. Extravascular pressure works in a linear fashion as well. As the pressure increases or decreases, extravascular pressure compresses or relaxes capillaries, venules, and veins, consequently exerting a controlling factor on blood flow. Myogenic response is dependent on changes in perfusion pressure. The smooth muscle of the resistance vessels contracts or relaxes depending on the perfusion pressure. The myogenic response of the vessels is also affected by intramural pressure, which exerts a slight vasodilatory effect on the vessels. Neural and neurohumoral factors exert indirect vasodilatory and vasoconstrictive effects on the resistance vessels. Increased blood flow is stimulated by sympathetic nerves, but the increase in flow is more directly caused by tachycardia as opposed to direct stimulation of the vessels. Sympathetic cholinergic innervation to the coronary vessels appears to be nonexistent, although there is experimental evidence that α- (constrictor) and β- (dilator) receptors exist on the vessels.

Carbon dioxide, oxygen, lactate, hydrogen ions, histamine, potassium ions, increased osmolarity, polypeptides, and adenosine nucleotides are myocardial metabolic substrates observed to have a regulating effect on coronary blood flow. As myocardial metabolism increases, the products of this metabolism increase, and one or several of these diffusible substances may exert a vasodilatory effect on the smooth muscle of the regulatory arteries and arterioles, thereby reducing arterial resistance. Conversely as myocardial activity decreases, arterial resistance increases. Experimental evidence seems to be in agreement with the theory that coronary blood flow is primarily regulated by myocardial metabolic requirements. This concept is based in part on the fact that coronary blood flow continues to regulate itself in the denervated heart. Since myocardial activity is dependent on high energy requirements, adenosine and oxygen have been suggested as the primary metabolites involved in the regulation of coronary blood flow.

Obviously any local control on the coronary blood vessels, irrespective of the substance responsible, requires an appropriate anatomic substrate. Some ex-
FIGURE 6. Photomicrographs of arterial-venous relationships that correspond to reconstruction in figure 5. In A, note branches of arteriole in the center. In B, note the envelopment of the arteriole by the vein.
pericellular studies have suggested that a countercurrent mechanism exists to regulate arterial resistance.\textsuperscript{5,6}

The observations made in this investigation support such an anatomic model in the human heart. Because of the close proximity of arteries to veins, diffusible substances carried in veins could have a direct effect on the diameter of the arteries. Figure 7, a composite schematic representation of the images in figures 1, 3, and 5, demonstrates this relationship. The diagram represents a blood flow pattern with increased myocardial activity. As myocardial activity increases, so do the end products of this metabolism and thus so does the blood supply. Dilatation of arteries could partially obstruct the accompanying vein, a relationship suggested in figure 6, B. The auxiliary venous system not adjacent to the arteries would be a possible alternative drainage route for the increased volume of blood flow and would prevent rapid washout of the end products of myocardial metabolism within juxta-arterial veins. Consequently, the myocardial metabolites would continue their vasodilatory effect on the arteries, allowing myocardial requirements to be maintained. It is also possible that substances carried in the arteries could diffuse directly to the veins. The observation that venous oxygen content changes little with changes in work could be accounted for, in part, by such a mechanism.

In conclusion, this study of arterial and venous relationships within the human left ventricular wall shows two venous systems, one closely related to arteries and one running within muscle fascicles well removed from the arteries in the interstitial spaces. This anatomic arrangement suggests the possibility of a countercurrent control of coronary artery flow by diffusible substances carried in the blood of juxta-arterial veins.

References

FIGURE 7. Coronary blood flow diagram. Arrows show direction of blood flow. Ovals depict the interstitial spaces. One set of veins has a countercurrent relationship to arteries and the other set is isolated within the muscle fascicle.
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