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# Coronary venous retroperfusion: an old concept, a new approach

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<sup>1</sup>Departments of Biomedical Engineering, Surgery, and Cellular and Integrative Physiology, Indiana University Purdue University Indianapolis, Indianapolis, Indiana; <sup>2</sup>Department of Cardiac Surgery, Austral University, Buenos Aires, Pilar, Argentina; and <sup>3</sup>Department of Medicine and <sup>4</sup>Indiana Center for Vascular Biology and Medicine, Indiana University School of Medicine, Indianapolis, Indiana

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**Kassab GS, Navia JA, March K, Choy JS.** Coronary venous retroperfusion: an old concept, a new approach. *J Appl Physiol* 104: 1266–1272, 2008. First published February 21, 2008; doi:10.1152/jappphysiol.00063.2008.—The potential of the coronary veins for revascularization has been evaluated by many investigators for more than a century. The major hurdle has been the damage of veins during sudden exposure to arterial pressure. The solution to this problem has typically involved the use of intricate and complicated apparatus and devices, which has prevented routine clinical utility in the catheterization laboratory. This review examines this old concept from a new perspective and proposes a novel hypothesis to address previous shortcomings. We speculate on an approach that may serve to eliminate the edema and hemorrhage that result during venous retroperfusion as the pressure is suddenly increased to arterial values. We propose the rationale to increase the venous pressure to arterial values more gradually to allow prearterializations of the veins before full exposure of arterial pressure. Finally, we discuss various possible indications for this selective autoretroperfusion strategy to combat myocardial ischemia in cardiogenic shock patients, ST-elevation myocardial infarct patients, no-option patients, and beyond.

coronary veins; remodeling; myocardial ischemia

## HISTORY AND OVERVIEW OF RETROPERFUSION: AN OLD CONCEPT

THE NOTION OF OXYGENATED arterial blood delivery through the coronary venous system (retroperfusion) to the ischemic myocardium dates back over 100 yr ago (40). In 1898, Pratt (34) developed the idea of perfusion of the heart muscle through the coronary sinus in isolated feline hearts. His work suggested that venous retroperfusion can provide some degree of nutritional delivery. In 1949, Beck (3) made the initial attempts of chronic retroperfusion of the coronary sinus by means of anastomosis to an arterial vessel [coronary venous bypass graft, (CVBG)]. In 1956, Lillehei et al. (26) were the first to use this technique during cardiac surgery for myocardial protection.

Coronary retroperfusion was quickly abandoned, however, because of structural damage of the coronary sinus wall as well as intramyocardial vasculature produced by drainage disruption and elevated pressures (40). Hemorrhage of the myocardium was reported as a complication during retroperfusion involving an arteriovenous shunt driven by an external roller pump through a catheter wedged in the anterior interventricular vein (48). These complications, in conjunction with the adoption of coronary artery bypass grafting (CABG) and the eventual development of percutaneous transluminal coronary angioplasty (PTCA), limited the retroperfusion concept and coronary sinus interventions clinically (40).

The advent of myocardial protection techniques using various cardioplegic solutions delivered in either antegrade (ascending aorta) or retrograde fashion has ushered in a revival of interest in the possible utility of retroperfusion (31, 32). Currently, the growth in off-pump revascularization techniques and recognition of the benefits of avoiding extracorporeal circulation has also stimulated interest in myocardial protection through the coronary sinus (40). Furthermore, Lazar and colleagues (22, 25) suggested that transient coronary venous pressure augmentation produced by coronary sinus occlusion (CSO) might provide cardiac circulatory support much like retroperfusion. There is now significant evidence that coronary sinus intervention rescues ischemic myocardium (23, 27) and restores myocardial contractile force (44).

In the past half century, there have been enormous advances in augmenting blood flow to the ischemic myocardium. The treatments of acute coronary syndrome are facilitated by the use of thrombolytic agents, PTCA, and CABG. Currently, interventional practice has been focused on restoring flow within the coronary arterial system where unstable atherosclerotic lesions are found. The use of the coronary venous system to provide perfusion to the coronary circulation has a potentially significant advantage, however, in that the veins are free of atherosclerotic disease even when the coronary arteries are severely diseased (1).

The objective of this review is to highlight a new approach to this old concept. We shall briefly review previous retroperfusion approaches and consider their efficacy in light of a functional venous anatomy. We also discuss data on a novel approach that may mitigate the pathological response known to

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occur in the venous system upon sudden exposure to arterial perfusion pressures. Finally, we explore the potential utility of this approach to providing circulatory support in two contexts: acute treatment of patients in cardiogenic shock or in patients with ST elevation myocardial infarct (STEMI), as a bridge to percutaneous coronary intervention; as well as chronic treatment for no-option patients with intractable angina.

#### RETROPERFUSION SYSTEMS

To date, a number of retroperfusion methods have been developed, some for acute treatment and others for chronic use. For acute treatment during ongoing injury, pressure-controlled intermittent coronary sinus occlusion (PICSO) has been used in conjunction with a balloon-tipped catheter positioned just beyond the orifice of the coronary sinus connected to a pneumatic pump (40). Synchronized retrograde perfusion (SRP) and simplified retroperfusion (SR) are other techniques that actively pump blood into the coronary sinus, from either an arterial or venous source in the former and the latter, respectively (40). The various systems used with CSO as a common denominator are intermittent coronary sinus occlusion (ICSO), PICSO, SRP, and SR. All coronary sinus interventions attempt to temporarily increase the coronary venous pressure or to provide retroperfusion of arterial blood. Hence, the redistribution of coronary sinus blood flow reaches the ischemic myocardium through changes in pressure gradients in the coronary venous system.

Although these various CSO-based approaches show significant efficacy in limiting myocardial damage (28, 40), they have not become routine clinical techniques largely because of the cumbersome devices requiring sophisticated pumps and the potential risks. For example, higher coronary sinus pressures are expected to occur because of the direct infusion of blood into the coronary sinus during diastole using SRP. Flow rates must be continuously monitored because they are critical for efficacy; less than optimal flow shows poor results, whereas very high flows are associated with pressure that damages the coronary sinus with thrombosis and eventual stenosis and chronic myocardial edema (24).

To our knowledge, two pumpless approaches have been described in recent years, both with potential for chronic application: 1) percutaneous in situ coronary venous arterialization (PICVA) and 2) stent-based ventricle-to-vein bypass (venous VPASS). PICVA is a catheter-based technique developed to provide arterial blood flow from the native coronary artery to the coronary vein while the outflow toward the coronary sinus is blocked (29, 35). The major limitation of this approach is the procedural complexity, requiring penetration of the arterial wall to access the nearby vein, which is often difficult in no-option patients with significant diffuse disease. Furthermore, this method creates a sudden increase in coronary venous pressure and may be associated with subsequent myocardial hemorrhage. The VPASS approach is also catheter-based, placing a stent based device designed to provide systolic blood flow directly from the left ventricle into either a coronary artery (4, 5) or a coronary vein (35). One limitation of this procedure is the necessity of selective catheterization of the veins draining the ischemic territory (35). A more fundamental limitation is the inability of this approach to provide complete perfusion of the subendocardium during systole. Furthermore,

the blood may be suctioned from the coronary venous system during diastole. Both PICVA and VPASS are irreversible procedures and hence can only be used chronically.

#### EFFICACY OF RETROPERFUSION APPROACHES

Hochberg and colleagues (15) surveyed surgeons who attempted to arterialize the coronary venous system using CVBG. The CVBG procedures were planned due to either 1) diffuse distal coronary disease, 2) small distal coronary arteries considered to be inappropriate to be grafted, 3) reoperative CABG procedures in which coronary arteries could not be visualized, and 4) intramyocardial coronary arteries in which no artery could be situated. The coronary vein was proximally ligated to the CVBG anastomosis in the majority of cases. The outcome was positive with improvement in the angina symptoms and very good patency rate.

Syeda et al. (40) produced a meta-analysis to evaluate the efficacy of ICSO and ICSO in combination with arterial blood retroperfusion (40). Over 100 animals were tested in 7 experimental trials to analyze the effects of ICSO on ischemic injury during coronary occlusion. The results of a meta-analysis evaluating the effect of ICSO and ICSO in combination with retroperfusion of oxygenated blood showed a significant reduction in infarct size in the treatment group compared with that of placebo group (40).

Acute ischemic damage to the myocardium originates and progresses as a transmural wavefront occurring initially in the subendocardium (Endo) (36). Consequently, ischemic myocardial damage is generally most severe in Endo. Any method that could augment myocardial blood flow in the ischemic region (especially in Endo) can be a valuable therapeutic approach in reversing myocardial ischemia (17). CSO during ischemia causes a significant enhancement in the Endo blood flow, reversing the Endo-to-epicardium blood flow ratio (17). This confirms that CSO offers myocardial protection, particularly in the Endo area where ischemia is more pronounced. One of the mechanisms for blood flow shift to the Endo by CSO may be related to the decreased intramyocardial pressure during CSO. Ido et al. (17) hypothesized that the combination of CSO and reperfusion decreases the severity of myocardial ischemia because of the alteration of the intramural distribution of coronary blood flow. Scharf et al. (39) found that an occlusion of the coronary sinus caused a redistribution of the venous flow to other channels emptying in the right heart.

Lillehei and colleagues (26) introduced retrograde coronary sinus perfusion during an aortic valve procedure, as an approach to protect the heart. The advantages of retrograde coronary sinus perfusion include the following: 1) the assurance of a fairly homogeneous cardioplegia delivery even when severe coronary artery disease is present; 2) successful retroperfusion even in the presence of aortic valve regurgitation or with an open aortic root, while avoiding the possibility of coronary ostial injury; 3) retrograde coronary sinus perfusion may wash out distal emboli (including air emboli) from the arterial system; and 4) the delivery may be continuous or intermittent during the surgical procedure. Despite these benefits, the effectiveness and protection of using retrograde coronary sinus perfusion alone for myocardial protection are still controversial, especially because of the lack of protection of the right ventricle (38).

New imaging techniques and catheter designs make possible a rapid access to the coronary sinus (11). Coronary sinus perfusion techniques have been established both experimentally and clinically to either delay or reverse ischemic changes, decrease infarct size, decrease myocardial hemorrhage and no-reflow phenomenon, and improve left ventricular function. The exact mechanisms by which coronary sinus retroperfusion salvages ischemic myocardium are not yet fully understood. It has been considered, however, that in addition to actual delivery of blood substrate to the ischemic myocardium, enhanced washout of toxic reactive oxygen metabolites, diminished granulocyte trapping, diminished cellular and interstitial edema, and diminished plugging of the microcirculation may all play a role (1). An additional new hypothesis regarding the role of a functional venous microcirculation will be explored below.

**ARCHITECTURAL BASIS FOR CORONARY RETROPERFUSION**

If the coronary venous system consists of only epicardial drainage into the coronary sinus (i.e., single arterial inlet and single venous outlet), then retroperfusion will result in stagnation of flow and an increase in venous pressure to arterial levels. Coronary retroperfusion is possible, however, because the coronary venous anatomy extends beyond the coronary sinus. There exist many Endo Thebesian vessels with communications or interconnections within each system and in between the two systems (2, 10, 12, 19, 47). Figure 1 illustrates a schematic of the coronary vasculature where the venous system has intervenous connections, Thebesian-sinus connections and a venous plexus. During coronary retroperfusion, some flow proceeds through the capillaries and to the arterial tree (*route 1*, Fig. 1). Alternatively, the flow may also distribute

through the venous plexus and drain into the Thebesians (*route 2*). Finally, the flow may be shunted away via intervenous or sinus-Thebesian connections (*routes 3 and 4*, respectively), depending on the level of the venous network at which retroperfusion is imposed.

The number of sinus-Thebesian anastomoses varies along the length of the coronary sinus. Perfusion of Microfil (polymer) at the left anterior descending (LAD) vein provides extensive filling of the venous system in the LAD artery territory as shown in Fig. 2A. A dense meshwork of venous vessels reaches the left ventricular subendocardium. Perfusion of polymer at the Great Cardiac vein (lateral wall of the left ventricle, Fig. 2B) shows a greater perfusion territory including the lateral wall but less dense filling at the LAD artery region. Microfil material was lost through venous interconnections that drained directly either into the ventricles or the right atrium. Finally, perfusion of vein near the coronary sinus results in yet broader perfusion territory including the right ventricle with significantly less perfusion of the left ventricle (Fig. 2C). Significant Microfil was found in the right atrium and ventricles (especially right ventricle). Hence, the site of selective retroperfusion is depended on the myocardial territory of interest (LAD, left circumflex, or right coronary artery disease) to provide targeted perfusion.

**TRANSPORT CAPACITY OF VENOUS MICROCIRCULATION**

Although the retroperfusion microsphere capillary flow only represents a small percentage of arterial flow (30), significant myocardial function is restored. It is interesting to consider how it might be possible to restore so much function with so little capillary flow? The answer may lie in the role of the venous microcirculation in oxygen and nutrient transport and

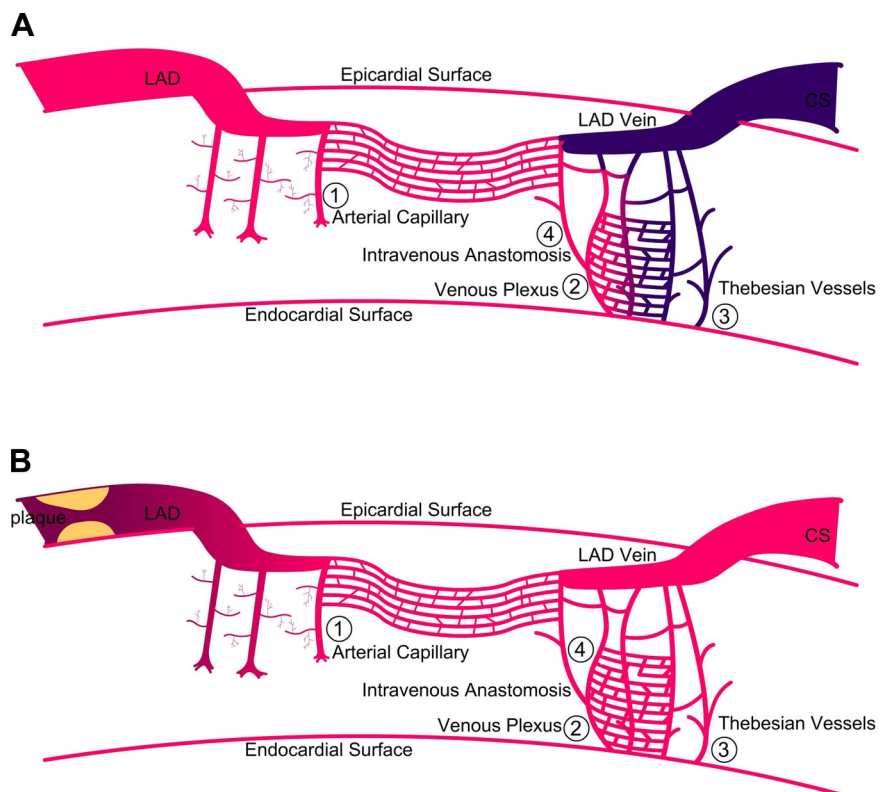


Fig. 1. A schematic of coronary circulation during antegrade (A) and retrograde (B) perfusion. Red denotes oxygenated arterial blood while blue represents venous blood. LAD, left anterior descending; CS, coronary sinus.

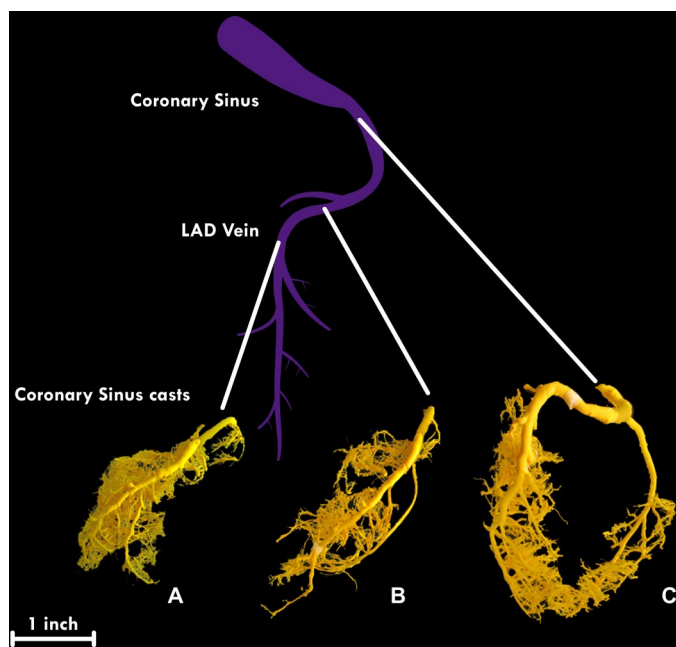


Fig. 2. Coronary vein cast obtained from retroperfusion at the LAD vein (A), great cardiac vein (B), and coronary sinus (C). The coronary venous system was cannulated at the respective position and casts were made from Microfil perfused at pressure of 40 mmHg.

waste removal. Because there are roughly two venules per each arteriole with generally larger diameters (19), the surface area of venules is significantly larger than that of arterioles (Fig. 3). Indeed, the venous microcirculation (*orders 0–4*,  $<60\ \mu\text{m}$  in diameter) has six times the surface area of the arterial capillaries. These data provoke a careful consideration of the possibility that oxygen and nutrient transport occurs throughout the venous microcirculation, in particular during retroperfusion.

Classically, it has been assumed that the unloading of oxygen from the blood to the tissue occurs primarily in the capillaries (41–43). However, data on longitudinal and radial oxygen gradients (8, 9) in the arteriolar network suggest that a significant amount of oxygen is lost from these vessels as well. In organs with low rates of metabolic activity, the arteriolar network appears to be the main site of oxygen delivery to the tissues, while organs with high metabolic activity (e.g., brain and myocardium) exhibit lower longitudinal  $\text{PO}_2$  gradients along the arteriolar blood vessels (43). The rate of oxygen loss from arterioles in either case is too large to be explained by diffusion alone. A possible explanation of this phenomenon is a high rate of oxygen consumption within the arteriolar wall (41).

The noncapillary vessel wall has been previously regarded as a barrier between the blood and the parenchyma that restricts the passage of macromolecules and allows exchange of gases (41). The vessel wall (mainly endothelium and smooth muscle cells) is the site of chemical synthesis and metabolic processes. Oxygen is the principal mediator in many homeostatic and disease processes in the vessel wall. It has been demonstrated that there is a substantial  $\text{O}_2$  loss from the blood as it passes through the arteriolar network, and a large  $\text{PO}_2$  gradient across the arteriolar vessel wall is probably caused by a large amount of  $\text{O}_2$  consumption within the endothelial and smooth muscle

cells as reviewed by Tsai et al. (43). In addition, Duling and colleagues (8, 9) have shown both a longitudinal gradient along the arterioles, capillaries, and venules and a transmural gradient across the wall of these vessels, which is compatible with the concept that the vascular wall behaves as an oxygen sink at all levels of the vascular tree (41).

If oxygen transport can occur beyond the thin-walled capillary vessels, is the venular wall thin enough to play a dominant role in this process? The wall thickness of arterioles of different orders or diameters at varying transmural myocardial positions is shown in Fig. 4A (7). Similar data are shown for the corresponding venules of sham and venous ligation hearts in Fig. 4, B and C, respectively. Clearly, the venous vessels in normal and venous-ligated hearts have significantly lower wall thickness than the corresponding arterioles. Interestingly, the wall thickness is relatively uniform throughout the coronary venous microcirculation owing to the relatively uniform pressure, and this is only roughly twice the thickness of the capillaries in both normal and venous-ligated hearts (Fig. 5). In summary, the significant surface area (Fig. 3) and the relatively walled-thin venous microvasculature (Figs. 4 and 5) can serve as an exchange unit during retroperfusion of arterial blood without significant radial losses in oxygen. Hence, there is more oxygen available during retroperfusion for the myocardial tissue compared with antegrade perfusion. These structural and functional features of the coronary venous microvasculature may explain the significant efficacy seen for retroperfusion even in the absence of substantial capillary flow (30).

#### NEW APPROACH: AUTORETROPERFUSION

Although coronary retroperfusion has become a clinical routine in many operating rooms for cardiopreservation during cardiac surgery, it has not been routinely adapted by the interventional cardiologist in the catheterization laboratory. The major reason is that previous percutaneous applications of the method require sophisticated apparatus and methods for implementation (intermittent occlusion, synchronized perfusion, etc.). The chronic utility of the approach for surgery (CVBG) has also been abandoned due to the observation of pressure-induced injury to the venous system and myocardium.

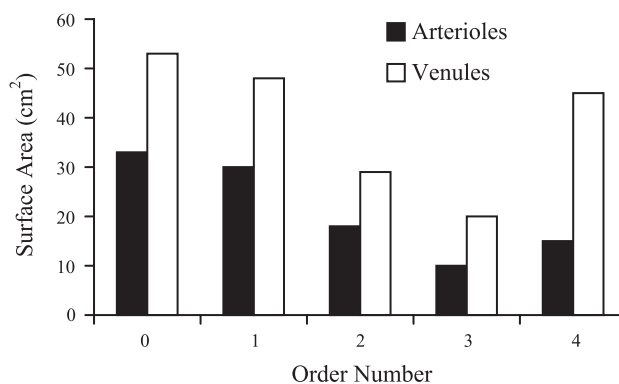


Fig. 3. Total surface of arterioles (from right coronary artery, LAD, and left circumflex trees) and venules (from sinusal and Thebesian trees) for the first several orders of vessels (1–4). The mean diameters for arterioles of *orders 1, 2, 3, and 4* are 9, 12.3, 17.7, and 30.5  $\mu\text{m}$ , respectively. Similarly, the mean diameters for venules of *orders 1, 2, 3, and 4* are 10.6, 16.5, 29.6, and 57.5  $\mu\text{m}$ , respectively. *Order 0* corresponds to arteriolar or venular capillaries.

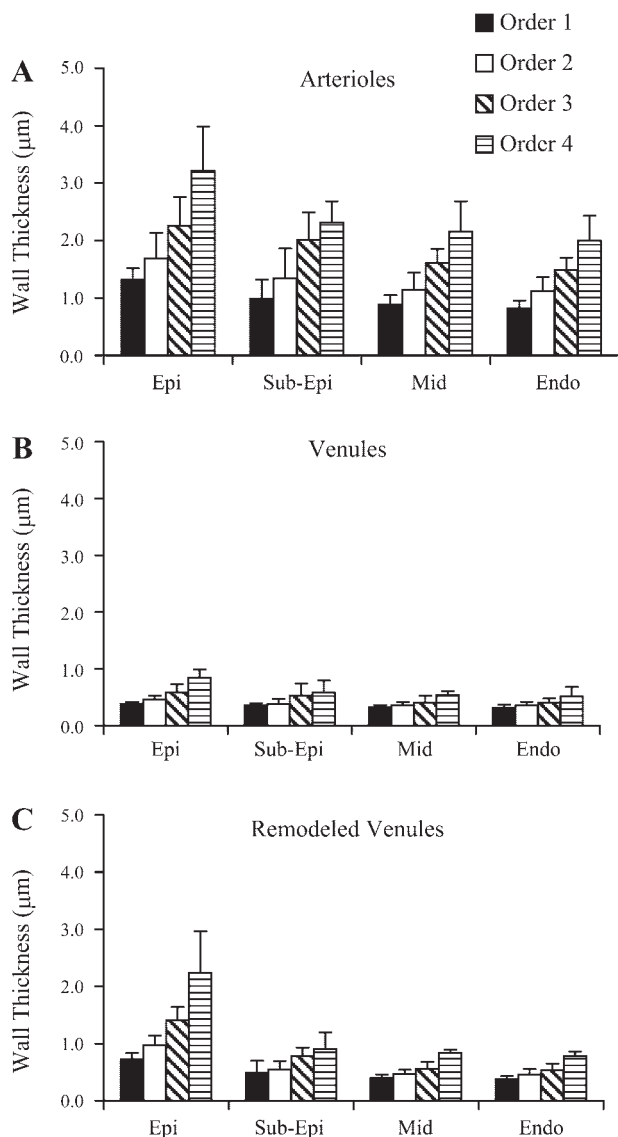


Fig. 4. Wall thickness (intima-media) of arterioles (A), venules (B), and venules (C) exposed to elevated pressures induced by venous ligation. Four transmural locations [epicardial (Epi), subepicardial (Sub-Epi), midwall (Mid), and endocardial (Endo)] were sampled for 4 different orders.

Clearly, there is a need for a new method that overcomes these and other shortcomings.

An ideal method to provide blood flow to the myocardium should not require external pumps or intricate devices but should utilize the patient's arterial own pulse pressure, i.e., autoretroperfusion (ARP). Furthermore, the method should be minimally invasive (percutaneous) and easily implemented. The ideal connection between an arterial source and the particular region of the coronary venous system (selective retroperfusion) via a catheter or cannula should reduce the pressure delivered to the venous system to a value below the rupture pressure. This could conceivably be tailored for each patient using a pressure transducer and flow probe embedded in the catheter. An implantable catheter possessing a variable stenosis could contribute regulation of pressure in the venous system over time to provide a more gradual increase in pressure. We have hypothesized that such a system would allow the

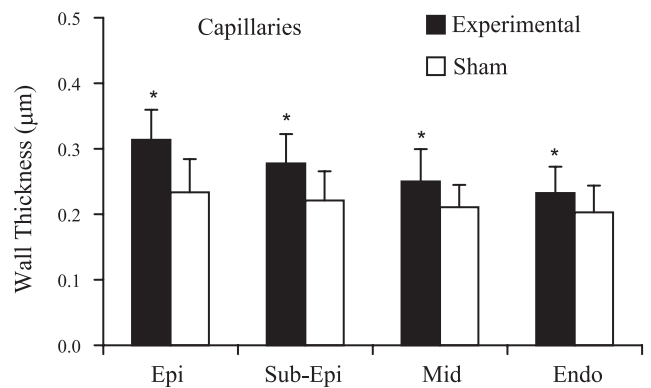


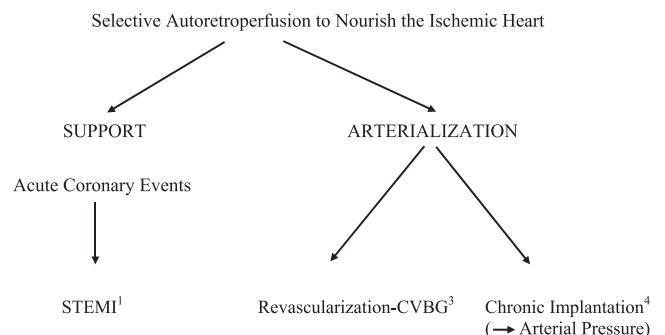
Fig. 5. Wall thickness of capillaries (<10  $\mu\text{m}$  in diameter) for control and venous ligation-induced pressure overload group.

venous vessels to arteriaize and the vessel walls to thicken to decrease the stress and prevent rupture of the postcapillary venules. We further hypothesize that a gradual increase in pressure would decrease the injury response and subsequently reduce the atherosclerotic changes that have been described in large epicardial veins subjected to supraphysiological pressures. Some of these hypotheses were validated as described below while others remain to be verified in future studies.

**PREARTERIALIZATION OF CORONARY VEINS FOR RETROPERFUSION**

Hammond and associates (13) established that severe injury to the coronary vein system initiates when pressure exceeds 60 mmHg. To remedy this issue during retroperfusion, it may be best to gradually increase the venous pressure to allow the system to arteriaize. To test the hypothesis that elevated venous pressure can cause venous remodeling, including increase in wall thickness, Choy and Kassab (7) ligated the great cardiac vein for a period of 2 wk to allow the LAD vein and its branches to structurally adapt to a mean pressure of 50 mmHg.

To identify the structural remodeling of the venous wall in response to intermediate increase in pressure, Choy et al. (6) ligated the LAD vein, thus raising the pressure in the proximal bed to intermediate levels between arterial and venous values (~50 mmHg). One study focused on the LAD vein to reveal



¹ICU or ER Physician; ²Interventional Cardiologist; ³CV Surgeon; ⁴Vascular Surgeon  
 Fig. 6. A schematic for potential utility of selective autoretroperfusion. STEMI, ST segment-elevation myocardial infarct patients; ICU, intensive care unit; ER emergency room; CV, cardiovascular.

that the structural remodeling of the vein was circumferentially nonuniform because the vein is partially embedded in the myocardium. The vein remodeling was also found to be axially non-uniform, because the vein is tethered to the myocardium to different degrees along its length (6). The response of the vein to increase in pressure depends on the local wall stress, which is in part determined by the surrounding tissue. Furthermore, the geometric remodeling of the coronary vein was found to restore the circumferential stress to the homeostatic value (20).

A second study focused on the coronary microvasculature. In the same animal preparation, myocardial tissue samples were obtained from the area adjacent to the LAD vein at four transmural locations of the left ventricular free wall: epicardial surface, subepicardium, midmyocardium, and endocardium. Each vessel was categorized in four different orders according to lumen diameter. The results show that intima-media thickness was larger in the experimental group in all four regions of the heart and in all four orders of the vessels, although venules from the epicardial region showed the largest increase in thickness. The greater arterialization of epicardial venules is fortuitous as those vessels experience larger transmural pressures during the cardiac cycle because of the lower intramyocardial pressure compared with endocardial vessels (6).

#### POTENTIAL CLINICAL UTILITY

There may be acute and chronic utility of coronary ARP in interventional cardiology and cardiac surgery (Fig. 6). Acutely (as a bridge treatment), STEMI patients (nearly 400,000 per year) may benefit from this approach (18). It is estimated that only a third of patients presented with an acute myocardial infarction are eligible for thrombolytic therapy or acute angioplasty procedures. Acute patients typically need to be transferred from either community hospitals or their own facility to the catheterization laboratory where emergency PTCA or CABG is offered. It has been recognized that the interval from the acute event to the actual angioplasty procedure (time to balloon) is an important predictor of the 30-day mortality (33, 45). The ARP may be important for preserving myocardial tissue viability and serve as a route to administer antiarrhythmics, thrombolytics, substrates, oxygen-free radical scavengers, inotropics, and cell and gene therapy to the jeopardized myocardium (14, 16). With the experience of coronary sinus catheterization gained by electrophysiologists through insertion of pacemaker lead, it is estimated that coronary sinus catheterization can be established in as little as 5 min (24) and can be potentially administered by an intensive care unit or critical care unit physician. Hence, ARP may be a valuable short-term method (bridge) for maintaining ischemic myocardium viability in patients awaiting coronary angioplasty or revascularization. Although this has been shown to be promising in animals (21, 30, 46), clearly further validation will be necessary.

ARP may also be implemented as a circulatory support during coronary angioplasty or cardiac operations especially for the cardiogenic shock patients (Fig. 6). In this context, retroperfusion has been shown to provide a valuable route for the homogeneous cardioplegic solution delivery during open-heart procedures in patients with diffuse atherosclerotic disease and poor runoff (37). The retroperfusion facilitates the preservation of tissue viability improving cardiac function. This may

be useful particularly as a treatment for “no-reflow” phenomenon (17).

For chronic application, the no-option patients may be the primary candidates (29). The ability of the venous system to significantly prearterialize (6, 7) within 2 wk suggests an interesting strategy for chronic ARP. We suggest that the ARP catheter should initially provide a pressure <60 mmHg to prevent shock of the venous system and allow prearterialization of the vasculature. After 2 wk, no-option patients could conceivably undergo bypass surgery for revascularization using CVBG, where the venous system is prearterialized and can withstand the arterial pressure (Fig. 6). For no-option patients who cannot undergo bypass surgery, the catheter stenosis may be released after two wk, so that the venous system would then be exposed to the full arterial pressure while the catheter remains permanently implanted. The chronic implantation of the catheter can be made in the axillary artery-vein system where a graft portion of the catheter can be surgically anastomosed with the artery. The validation of this approach for chronic applications awaits future studies.

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