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EXPERIMENTAL STUDIES

Selective Perfusion of Ischemic Myocardium During Coronary Venous Retroinjection: A Study of the Causative Role of Venoarterial and Venoventricular Pressure Gradients

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Coronary venous retroinjection is often associated with preferential distribution of flow to ischemic myocardium. The purpose of this study was to define the mechanism of such retrodistribution of flow. In 24 anesthetized open chest dogs, Monastral blue dye (10 ml) was injected by way of a balloon catheter in the distal great cardiac vein as a marker for retrograde flow distribution. The injection rate (0.6 to 2.4 ml/s) was adjusted such that systolic pressure in the anterior interventricular vein ranged between 60 and 85 mm Hg. In 11 dogs with no ischemia and normal myocardial perfusion pressure (96 ± 8 mm Hg), no myocardial staining occurred despite retrograde filling of epicardial veins. One minute after occlusion of the left anterior descending coronary artery, dye injections caused selective staining of the cyanotic area in 15 of 18 episodes, sparing the normal myocardium within the zone of retroperfused veins. In five dogs, with the arterial pressure <55 mm Hg, retroinjection resulted in homogeneous staining of all the myocardium drained by the retroperfused veins.

Selective staining of the ischemic myocardium caused by retroinjection was associated with the following pressure gradients: during systole from the anterior interventricular vein to the occluded coronary artery, 31 to 58 mm Hg, and during diastole from the retroperfused veins to the left ventricular chamber, 9 to 28 mm Hg. There was no diastolic venoarterial gradient in the ischemic myocardium. In normal myocardium, retroinjection did not reverse the arteriovenous pressure gradient.

In conclusion, retrograde flow is primarily directed to myocardium with low anterograde perfusion pressure. Selective retrograde penetration of acutely ischemic myocardium can thus be achieved by a mechanism consistent with the development of venoarterial and venoventricular pressure gradients.

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The use of the coronary sinus as an alternative route for delivery of blood or drugs to ischemic myocardium has gained renewed interest (1–16). These interventions include synchronized retroperfusion (1–7), pressure-controlled intermittent coronary sinus occlusion (8,9) and coronary venous retroinjection (10–16). Preferential distribution of retrograde coronary venous flow to the ischemic myocardium (3,10,12,13,15) with variable degrees of distribution to normal myocardium (3,10,12) has been observed. Because the coronary venous pressure is increased in some portion of the cardiac cycle (1,2,4,8–10,15), the distribution pattern probably depends, at least in part, on the pressure gradients

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developed between the coronary veins and arteries. Although these pressure gradients clearly vary during the cardiac cycle, coronary occlusion and systemic hypotension, the relation of pressure gradients to myocardial retroperfusion has never been defined. Specifically, the conditions under which selective distribution of a retrograde injectate to ischemic myocardium occurs have not been established.

Consequently, the purposes of the present study were: 1) to delineate the distribution patterns of coronary venous retroinjections under various conditions of anterograde perfusion pressure, 2) to measure pressure changes in the distal coronary veins during retroinjection, and 3) to define the pressure gradients associated with selective distribution of retrograde injectates to ischemic myocardium.

Methods

Experimental preparation. Twenty-four adult mongrel dogs of either sex, weighing between 19 and 29 kg, were premedicated with morphine sulfate (1 mg/kg body weight intramuscularly) and anesthetized with sodium pentobarbital (30 mg/kg intravenously). Supplemental morphine and pentobarbital were given when necessary. After endotracheal intubation, respiration was maintained by a Harvard respirator with an expiratory pressure of 4 cm H_2O. The chest was opened through the left fifth intercostal space, and the heart supported in a pericardial cradle. In 13 dogs, the left anterior descending coronary artery was isolated and a suture passed around it. Transient occlusions were achieved by passing the two ends of the suture through a short piece of polyethylene tubing and abutting it against the artery (17). Care was taken not to damage or obstruct the accompanying veins. In the remaining 11 dogs, transient occlusion of the left anterior descending coronary artery was achieved by inflating a 2.5F double lumen balloon catheter introduced through the left carotid artery. This allowed measurement of pressure distal to the site of occlusion. The site of occlusion was distal to the first diagonal branch and in one to two test occlusions (30 seconds each) adjusted such that it produced a well delineated area of cyanosis. A 7F double lumen balloon catheter was introduced into the great cardiac vein through the coronary sinus and advanced until the tip was 8 to 16 mm proximal to the bifurcation of the anterior interventricular vein. After the balloon inflation with 0.6 to 0.9 ml air to prevent backflow to the right atrium, great cardiac vein injections of 10 ml saline solution (rates of 0.4 to 2.5 ml/s) were made through this catheter. The injections were made from a hand-held syringe, and the average rate of injection was calculated from time marks.

For pressure measurements in the proximal anterior interventricular vein, a second catheter (5F, single lumen with an endhole and two sideholes) was advanced in nine dogs via the coronary sinus so that its tip was located 5 to 9 mm distal to the tip of the great cardiac vein balloon catheter (Fig. 1a). During great cardiac vein occlusion without retroinjection, the pressure recordings of both catheters were identical in all dogs, indicating a reliable pressure recording even in the relatively small anterior interventricular vein. Systemic pressure was recorded in all dogs from the ascending aorta, and in six dogs the left ventricular pressure was also monitored by a 7F pigtail catheter.

Before instrumentation, intravenous heparin (50 IU/kg) was given, and all catheters were flushed at regular intervals with 10 IU/ml heparin-saline solution. All pressures were measured by Statham P23Db transducers (positioned at the midlevel of the heart) and recorded together with surface electrocardiographic (ECG) lead III on an oscilloscopic and photographic recorder (Electronics for Medicine, model VR 16).

An outline of the epicardial coronary veins was obtained with fluoroscopy during great cardiac vein retroinjections of sodium and meglumine diatrizoate (Renografin-76; 5 ml in 10 ml saline solution). These fluoroscopic images were recorded on a four head video recorder (Toshiba) and later played back and analyzed in slow motion. During injection, retrograde filling of the anterior interventricular vein and its branches was observed with no leakage at the site of great cardiac vein balloon occlusion. Special attention was paid to anterograde filling of anterolateral and posterior veins. These veins are filled to a variable extent by means of branches of the anterior interventricular vein and drain into the coronary sinus or the great cardiac vein proximal to the site of occlusion (Fig. 1a).

Experimental Protocol

Pressure measurements. The pressure in the anterior interventricular vein was evaluated before and 10 seconds after great cardiac vein occlusion (Fig. 2). At this time, the systolic pressure in the anterior interventricular vein had reached a plateau in all dogs. Pre- and postocclusion pressures in this vein were also obtained 1 minute after coronary occlusion. In six dogs, the systolic and diastolic pressures in the anterior interventricular vein were recorded during great cardiac vein injection at various rates (volume, 10 ml saline solution; rate, 0.4 to 2.5 ml/s). These injections were made 1 minute after occlusion of the coronary artery, with the great cardiac vein occlusions started 10 seconds before injection. Systolic and diastolic pressures in the left anterior descending coronary artery distal to the occlusion site were also expressed as a percent of systolic or diastolic aortic pressure, respectively (1). Four to six repeat coronary artery occlusions (90 seconds each) were made in each dog, with 15 minutes of recovery period in between.

In vivo dye injections. Monastral blue dye (E.I. DuPont de Nemours) was used to delineate the myocardial regions perfused by coronary venous retroinjection. This dye has been used as a marker for normal myocardial flow (18,19)

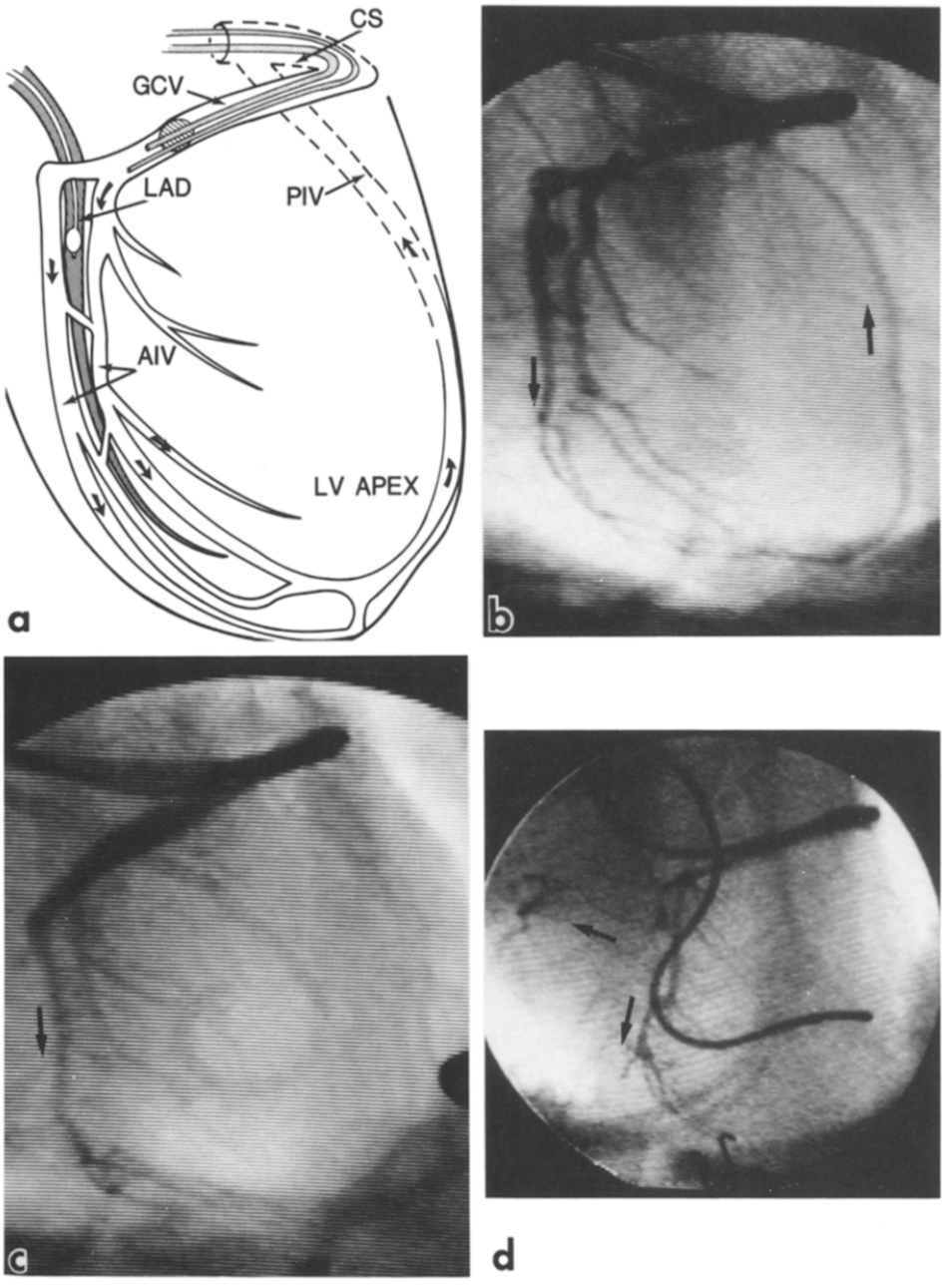

Figure 1. a, Schematic drawing of the coronary venous anatomy of the heart (left lateral aspect) and the catheter positions for retroinjection and pressure measurement. The flow of the injectate is indicated by **arrows**; note retrograde filling of the anterior interventricular vein (AIV) and anterograde flow in the posterior interventricular vein (PIV). **b, c** and **d,** Fluoroscopic images during injection of Renografin-76 into the distal great cardiac vein (GCV) (same projection as in **a**). In **b,** there is rapid and intense filling of a relatively large posterior vein (**right arrow**), whereas in **c,** two small posterior veins are barely filled. In **d,** only a small venovenous connection to a right ventricular vein is found (**upper arrow**). CS = coronary sinus; LAD = left anterior descending coronary artery; LV = left ventricle.

and for visualization of retrograde flow distribution after coronary venous retroinjection (13). In this study, great cardiac vein injections (2 ml Monastral blue in 10 ml saline solution) were made at a rate of 0.8 to 2.4 ml/s in the open chest preparation. The great cardiac vein was occluded 10 seconds before injection, and the balloon was released 1 minute after completion of injection. The distribution of the dye was observed during the injection, and the epicardial distribution was assessed 20 seconds after completion of injection.

Twenty-four dogs were assigned to three protocols for Monastral blue dye retroinjection. In protocol 1 (controls, n = 13), the aortic blood pressure was normal (systolic 92 ± 7 [range 80 to 125] mm Hg), and the coronary artery was not occluded. In protocol 2 (n = 20), the aortic blood pressure was normal and the left anterior descending coronary artery was occluded. The edge of the resulting cyanotic area and its relation to the local vasculature were used as an epicardial reference for dye distribution (20,21). In 6 of the 20 dogs, color photographs were taken to delineate the relation of epicardial dye distribution with respect to the cyanotic area. In protocol 3 (n = 5), the systolic aortic blood pressure was <55 mm Hg (range 40 to 55) and the left anterior descending coronary artery was occluded. In this group, three of the five dogs showed systemic hypotension after a previous dye injection, and two required additional administration of intravenous pentobarbital (20 to 40 mg/kg) to induce hypotension.

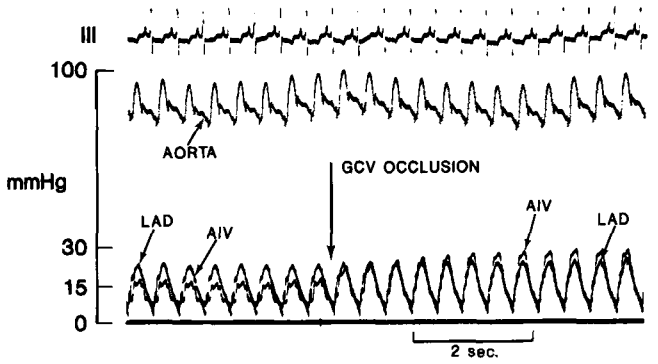

Figure 2. Effect of great cardiac vein (GCV) occlusion on the pressure in the anterior interventricular vein (AIV) in a dog with left anterior descending (LAD) coronary artery occlusion. After occlusion of the distal great cardiac vein (**long arrow**), the pressure in the anterior ventricular vein increases from 8/4 mm Hg to plateau values of 25/3 mm Hg. The pressure in the coronary artery distal to the occlusion site remains unchanged (21/5 mm Hg). III = surface electrocardiographic lead III.

Monastral blue dye injections were given 1 minute after coronary artery occlusion. Repeat dye injections were made in 11 dogs to compare distribution patterns at different hemodynamic states within the same dog. Coronary venous pressures were recorded during dye retroinjection, and injections rates were chosen such as to raise the anterior interventricular vein systolic pressure to values between 60 and 85 mm Hg.

Histopathologic examination. Nine dogs were killed within 1 to 2 minutes of dye injection, and the hearts were rapidly excised. After flushing off of blood and excess dye with saline solution, the hearts were cut transversely into 1 cm thick slices from base to apex for determination of the pattern of transmural dye distribution. For histologic evaluation, transmural sections of 6 μ thick were cut and stained with hematoxylin-eosin. Sections included the center and borders of stained tissues with inclusion of adjacent nonischemic regions that on gross inspection did not contain dye.

Statistical analysis. Continuous Gaussian variables are summarized as mean values ± standard deviation. The relation between the anterior interventricular vein pressure and the rate of great cardiac vein injection was analyzed in individual dogs using linear regression analysis and correlation (22). Because of the nonindependence of these data points, no probability (p) values are reported for the correlation coefficients. Sequential measurements of the coronary venous pressure were compared using Friedman's nonparametric analysis of variance for repeated measurements, followed by multiple comparisons using the Neuman-Keuls test. All statistical tests were carried out using an alpha level of 0.05.

Results

Epicardial venovenous shunts. During retroinjection of Renografin-76 solution, the anterior interventricular vein and its branches could easily be visualized. However, great variability from dog to dog was found in the number and size of anterolateral or posterior veins, or both, showing anterograde filling through venovenous connections (Fig. 1a). The extent of these venovenous shunts ranged from none to clear-cut filling of one or two large veins draining into the proximal great cardiac vein or the coronary sinus (Fig. 1b to d). In most dogs (11 of 15), anterograde filling of two relatively small posterior veins was found. In three dogs, a single relatively large posterior vein with massive shunting to the coronary sinus was identified.

Pressures in the anterior interventricular vein and great cardiac vein occlusion (Table 1). In the control state, the median pressure in the anterior interventricular vein was 11/3 mm Hg. Ten seconds after great cardiac vein occlusion, these pressures rose to 29/5 mm Hg and remained stable.

Table 1. Effect of Great Cardiac Vein Occlusion and Left Anterior Descending Coronary Artery Occlusion on Pressure in the Anterior Interventricular Vein

	LAD Open		LAD Occluded		
	Control	GCV Occlusion	Control	GCV Occlusion	Lad Dist
AIV pressure (mm Hg)					
Systole					
Median	11	29*	9‡	21†	24
Range	(7–23)	(20–51)	(6–19)	(16–30)	(17–24)
Diastole					
Median	3	5	2	4	8
Range	(1–5)	(2–8)	(1–5)	(3–7)	(6–12)

*$p < 0.05$ compared with control; †$p < 0.05$ compared with great coronary vein (GCV) occlusion with the left anterior descending (LAD) coronary artery open; ‡p = not significant compared with control with the left anterior descending coronary artery open. Numbers in parentheses indicate range. AIV = anterior interventricular vein; LAD dist = pressure in the left anterior descending coronary artery distal to occlusion.

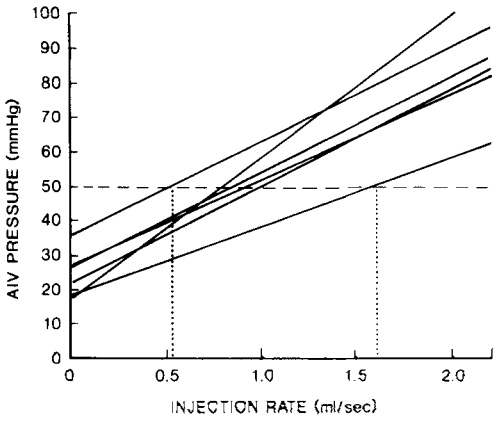

Figure 3. Regression lines of the systolic anterior interventricular vein (AIV) pressure versus rate of retroinjection in six dogs with left anterior descending coronary artery occlusion. In each dog, the correlation coefficient was greater than 0.85. The **vertical dotted lines** indicate the range of injection rates associated with a systolic anterior interventricular vein pressure of 50 mm Hg.

One minute after coronary artery occlusion with no great cardiac vein occlusion, the pressures in the anterior interventricular vein were not significantly different from the control state. When great cardiac vein occlusion and coronary artery occlusion were combined, there was a significant ($p < 0.05$) but less pronounced (21/4 mm Hg) increase in venous pressure (Fig. 2).

Pressures in the anterior interventricular vein during great cardiac vein retroinjection. During continuous saline retroinjection, there was an increase in systolic coronary venous pressure, reaching a plateau after three to five beats. The concomitant increase in diastolic pressure approached a steady state in a similar fashion. All subsequent pressure measurements were made at these steady state levels. In six dogs with coronary artery occlusion, the pressure in the anterior interventricular vein was monitored during retroinjections at different rates. A linear relation ($r > 0.86$) between the rate of injection and systolic coronary venous pressure was found in each dog. Although a high correlation coefficient was observed in each dog, the systolic pressures at a given rate of injection varied considerably from dog to dog (Fig. 3).

Diastolic pressures in the anterior interventricular vein showed less increase during retroinjection than did the systolic pressures. In general, at injection rates of less than 1.2 ml/s, the diastolic anterior interventricular vein pressures were below 32 mm Hg in all dogs with coronary artery occlusion. A linear relation ($r > 0.76$) between the rate of injection and the diastolic coronary venous pressure was found in five of the six dogs. In the remaining dog, the increase in diastolic pressure did not appear to be different from zero ($r = 0.55$, $y = 3.2 + 4.4x$).

The heart rate during either coronary venous occlusion or occlusion followed by coronary venous retroinjection remained unchanged in all dogs studied (Fig. 2 and 4). The mean heart rate was 137 ± 18 beats/min. In two dogs, the anterior interventricular pressure was measured during coronary venous retroinjection at two different heart rates—120 beats/min (spontaneous) and 180 beats/min (atrial pacing). The anterior interventricular vein pressure during a given rate of retroinjection remained unchanged by changes in the heart rate.

Retrograde dye distribution. A representative example of the outcome of protocols 1 and 2 is presented in Figure 5. In Figure 5a, the heart is shown during retroinjection of Monastral blue at normal aortic blood pressure with no coronary artery occlusion (protocol 1). At no time during

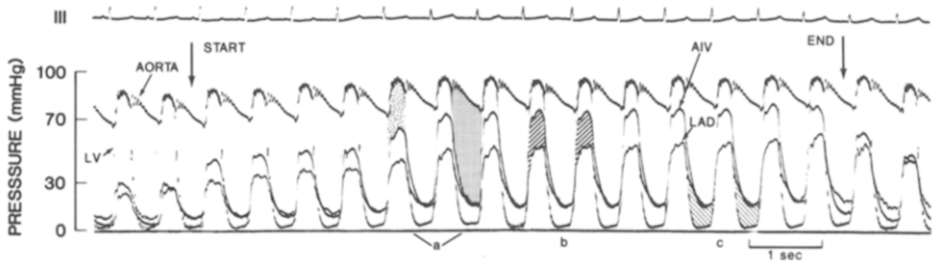

Figure 4. Pressure gradients during Monastral blue dye retroinjection leading to selective staining of the ischemic area. The start and end of injection (volume 10 ml, rate 1.1 ml/s) are indicated by **arrows.** Note that during retroinjection, aortic systolic and diastolic pressures are higher than in the anterior interventricular vein (AIV) (**a**). In contrast, however, the systolic anterior interventricular vein pressure exceeds that of the left anterior descending (LAD) coronary artery distal to occlusion (**b**), whereas in diastole they are equal. In **c**, a diastolic pressure gradient is evident between the anterior interventricular vein and the left ventricular (LV) chamber. The **hatched areas** in **a, b** and **c** denote the magnitude of the respective pressure gradients. For further details see text.

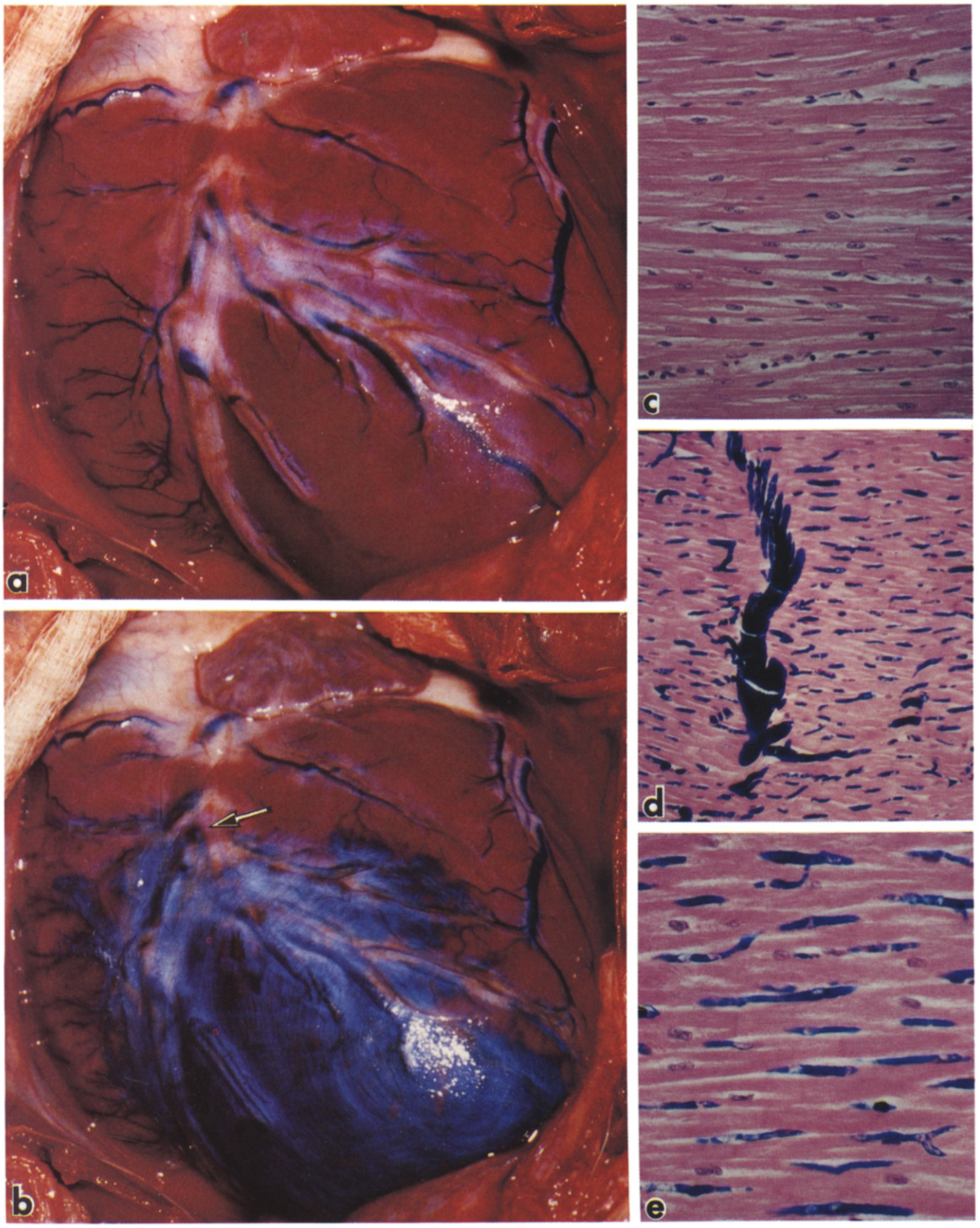

Figure 5. Morphologic findings of myocardial dye distribution. **a,** Gross photograph of control heart with no coronary artery occlusion. Note that epicardial veins fill during retroinjection, but there is no myocardial staining. **b,** Surface of dog heart with left anterior descending coronary occlusion (at site of **arrow**). Note that myocardial staining as well as venous staining is present. **c,** Histologic section from anterior wall of the left ventricle from a control dog, showing no staining. **d,** Section of anterior wall of the left ventricle from heart in **b,** showing blue dye in capillaries as well as in a subendocardial sinusoid. **e,** Higher power photomicrograph showing blue dye in capillaries (hematoxylin-eosin stain; original magnifications: **C** and **D** × 40, **E** × 100, all reduced by 16%).

and after the injection was there any myocardial staining, despite the obvious filling of the veins with the dye.

In Figure 5b, the injection is repeated in the same dog 1 minute after occlusion of the left anterior descending coronary artery. This resulted in a cyanotic area distal to the site of occlusion (not shown). Under this condition, only the cyanotic area became stained after great cardiac vein retroinjection. The nonischemic myocardium remained unstained even though it was within the drainage area of the anterior interventricular vein. As in Figure 5a, the epicardial veins over the normal myocardium showed retrograde filling. During hypotension, the dye retroinjection resulted in homogeneous staining of all the myocardium drained by the great cardiac vein.

Three common types of distribution patterns were observed with the three different protocols of great cardiac vein retroinjection: 1) no myocardial staining (despite retrograde filling of epicardial veins) in protocol 1 (n = 11); 2) selective staining of the ischemic area during protocol 2 (7 of 10); and 3) complete staining of the myocardium drained by the anterior interventricular vein during protocol 3 (n = 2). In three dogs in protocol 2, however, additional staining of normal myocardium occurred. It was localized at the site of the balloon of the great cardiac vein catheter (two dogs) (Fig. 1a), and the staining was adjacent to the border of ischemia (one dog).

Functional influences on distribution pattern. To determine whether different distribution patterns within the confines of a given coronary venous anatomy could be observed, repeat dye injections were performed in 11 dogs by sequentially changing the protocol of injections. In two dogs, all three protocols could be completed; in eight dogs, a dye injection in the control state (protocol 1) was followed by a second dye injection after coronary occlusion during normal aortic pressure (protocol 2). Incomplete dye washout from previous dye injections, however, allowed evaluation only of areas that had not been stained during prior dye injections. Even in the same dog, the three protocols of retroinjection were associated with different patterns of dye distribution. Typically, no staining was found before coronary occlusion at normal aortic blood pressure, whereas staining of the ischemic area was found during the repeat dye injection after left anterior descending coronary artery occlusion (Fig. 5a and b). Because no differences in the types of staining patterns were found between the initial and subsequent repeat injections in all dogs, the staining results were grouped (Table 2).

Table 2. Patterns of Monastral Blue Dye Distribution After Great Cardiac Vein Retroinjection

	Protocol 1 (n = 13)	Protocol 2 (n = 20)	Protocol 3 (n = 5)
No myocardial staining	13*	0	0
Selective staining of ischemic area	0	17	0
Complete staining of AIV territory	0	3†	5

*Number of dogs; †incomplete staining of normal myocardium in the anterior interventricular vein territory in addition to complete dye penetration of the ischemic myocardium. The numbers include the repeat dye injections. AIV = anterior interventricular vein.

Analysis of stained myocardial tissue. Left ventricular transverse slices (1 cm thick) in nine dogs showed that staining was transmural wherever it was observed on the epicardium. Although the overall intensity of staining varied considerably from dog to dog, the borders were sharply delineated even when staining was not intense. The staining was homogeneous in six dogs, and patchy in the other three, with areas of intense staining (diameter 4 to 8 mm) separated by less stained myocardium. Histopathologic evaluation (n = 5) of ischemic myocardium after protocol 2 showed filling of capillaries with blue dye particles throughout the myocardial wall (Fig. 5d and e). These color pigments were also found in the occluded coronary artery as well as in venous structures (diameter 80 to 300 μ) close to the endocardium (Fig. 5d), resembling the intramyocardial sinusoids (34,37,39). No color pigments could be found in the arterioles in both protocols 2 and 3. In contrast, in normal myocardium within the drainage area of the retroperfused veins, color particles could be found only in the epicardial veins (Fig. 5c). There was no interstitial myocardial extravasation of the blue dye. In two dogs, hemorrhage was found at the site of balloon occlusion around the distal great cardiac vein.

Pressure gradients during retroinjection. With no coronary artery occlusion and normal aortic blood pressure (protocol 1), the increase in systolic anterior interventricular vein pressure during saline retroinjection remained below arterial pressure. This was also the case for the diastolic coronary venous pressures. The range of the systolic gradient was 23 to 55 mm Hg, and that of the diastolic gradient 60 to 89 mm Hg. Thus, the direction of the normal arteriovenous pressure gradients was preserved, although diminished in magnitude. The pressure gradients found during dye injection in protocol 1 were similar to those seen during saline injections.

With coronary artery occlusion at normal aortic blood pressure (protocol 2), three pressure gradients could be identified during retroinjection. These pressure gradients differed in their anatomic location and their relation to the cardiac cycle (Fig. 4). In the nonischemic myocardium within the territory of the retroperfused vein, a pressure gradient was observed between the nonoccluded part of the coronary artery, that is, the aortic pressure (shaded area a in Fig. 4) and the coronary vein. This gradient closely resembled the gradient found before coronary occlusion.

In the ischemic myocardium, two pressure gradients were found during retroinjection. In systole, there was a pressure

Table 3. Coronary Artery and Venous Pressures and Related Pressure Gradients During Monastral Blue Dye Retroinjection in Five Dogs With Left Anterior Descending Coronary Artery Occlusion

Dog No.	Injection Rate (ml/s)	AIV (mm Hg)	LAD Sys (%)	LAD Dia (%)	AIV–OccLAD (mm Hg)		AIV–LV Dia (mm Hg)	Aorta (mm Hg)
					Sys	Dia		
1	2.4	84/18	30 (+9)	13 (+6)	52	2	14	106/82
2	0.6	50/12	25 (+12)	17 (+5)	31	0	9	75/54
3	1.0	70/20	28 (+26)	14 (+23)	48	0	17	80/54
4	1.0	85/32	23 (+2)	19 (+4)	58	11	28	118/90
5	1.1	74/16	33 (+24)	16 (+5)	42	0	12	96/74

The numbers in brackets indicate the increase in normalized pressures during injection. AIV = pressures in the anterior interventricular vein during systole and diastole, respectively; AIV–LV = diastolic gradient between the anterior interventricular vein and left ventricular chamber; AIV–OccLAD = gradient between the anterior interventricular vein and the occluded left anterior descending coronary artery. Inj. rate = rate of Monastral blue dye injection, leading to selective staining of the ischemic area. LAD Sys and LAD Dia = normalized pressures in the distal occluded left anterior descending coronary artery during systole and diastole.

gradient between the anterior interventricular vein and the occluded left anterior descending coronary artery. This gradient was about 12 to 30 mm Hg and was venoarterial in direction (shaded area b in Fig. 4). In diastole, there was a gradient between the epicardial veins and the left ventricular chamber (shaded area c in Fig. 4), with higher pressures in the former. Table 3 lists the pressures in the anterior interventricular vein, in the left anterior descending coronary artery distal to the occluded site and the associated pressure gradients in five dogs during Monastral blue dye retroinjection, leading to selective staining of the ischemic area. In four of the five dogs, there was no diastolic arteriovenous pressure gradient in the ischemic area. In one dog, a diastolic venoarterial gradient of 10 to 35 mm Hg was observed that resulted in intense staining of the ischemic myocardium. The diastolic gradient, however, was accompanied by anterior interventricular vein systolic pressures of up to 112 mm Hg. During retroinjection, the normalized pressures of the occluded coronary artery showed an increase, which was usually more pronounced during systole.

For a more detailed analysis, these gradients were evaluated during saline retroinjections at different rates 1 minute after coronary occlusion. The results were grouped according to the systolic coronary venous pressures (Table 4). With higher systolic venous pressures, there was a higher systolic gradient between the anterior interventricular vein and the left anterior descending coronary artery distal to the occluded site. Similarly, with higher systolic venous pressures, the diastolic gradient between the retroperfused vein and the left ventricular chamber was elevated. This gradient existed in normal as well as in ischemic myocardium of the retroperfused zone. In the normal myocardium, however, it was paralleled by the several times larger diastolic gradient from the nonoccluded coronary artery (represented by the aortic pressure) to the left ventricular chamber (Fig. 4).

Discussion

This study describes the influence of anterograde perfusion pressure on the patterns of myocardial retrodistribution during coronary venous retroinjection. For the first time, various distribution patterns are related to myocardial

Table 4. Pressure Gradients During Great Cardiac Vein Retroinjection of Saline Solution in Dogs With Occlusion of the Left Anterior Descending Coronary Artery

AIV Sys	Inj. Rate (ml/s)	Systole		Diastole		
		AIV–OccLAD	AIV–Aorta	AIV, OccLAD	AIV–LV	Aorta–LV
50–69 (n = 6)	0.6–2.0	20 ± 4	−43 ± 7	0.3 ± 6	8 ± 6	73 ± 6
60–69 (n = 5)	1.0–2.2	28 ± 5	−30 ± 5	4.4 ± 10	16 ± 11	68 ± 3
70–85 (n = 4)	1.0–2.0	31 ± 10	−22 ± 10	10.0 ± 10	21 ± 11	75 ± 9

All pressures are in mm Hg. AIV Sys = systolic pressure in the anterior interventricular vein during retroinjection; AIV–Aorta = gradient between anterior interventricular vein and aorta, representing the pressure in the nonoccluded left anterior descending coronary artery; Aorta–LV = gradient between aorta (representing the pressure in the nonoccluded left anterior descending coronary artery) and left ventricular chamber; other abbreviations as in Table 3.

pressure gradients. The major finding of this study is that selective distribution of a retrograde injectate to ischemic myocardium can be achieved provided appropriate coronary vascular pressure gradients develop.

Retroinjection and the normal myocardium. Myocardium with normal arterial perfusion pressure is not retroperfused when coronary venous pressure during retroinjection is kept below arterial pressure. Although the normal arteriovenous pressure gradient is diminished, its direction remains unaltered throughout the cardiac cycle, preventing retrograde delivery of the dye to the myocardium. In control dogs, in which retrograde dye delivery did not occur, extensive venovenous shunting as a cause was ruled out by the positive staining found when injections were repeated in the same dogs during coronary artery occlusion (that is, with lowered coronary pressure).

Retroinjection and the ischemic myocardium. Ischemic myocardium within the drainage area of the retroperfused veins was usually selectively stained, whereas normally perfused myocardium remained unstained despite its greater proximity to the injection site. This distribution pattern was found in the majority (17 of 20) of the dogs and constitutes the characteristic feature of this intervention. As in the control dogs, the arteriovenous pressure gradient in normally perfused regions of the myocardium was preserved, although diminished in amplitude. In contrast, during retroinjection, the arteriovenous gradient in the ischemic myocardium was reversed during systole (that is, the venous pressure exceeded the arterial pressure by as much as 58 mm Hg). This was usually not the case during diastole. There was, however, a gradient between the epicardial veins and the left ventricular chamber during diastole. The direction of both of these pressure gradients in the coronary vasculature is consistent with the observed pattern of selective staining of the ischemic myocardium.

Staining of myocardium outside the ischemic area, when found close to the site of retroinjection, could be due to local damage to the venous system. This damage, in turn, could have been caused by mechanical trauma from the repeat balloon inflations or by advancing the second catheter for the pressure measurements, which often required prolonged manipulation. Furthermore, a jet effect with high injection rates could conceivably cause damage even at moderately elevated pressures in the venous system. We have no explanation for the staining adjacent to the border of the ischemic zone seen in one dog. During this retroinjection, however, the venous pressure could not be measured for technical reasons, and excessively high pressure might have been reached.

During systemic hypotension, there was a pressure gradient (20 to 35 mm Hg) from the retroperfused veins to both the occluded and nonoccluded territory of the left anterior descending coronary artery. This could account for the staining pattern that comprised the whole retroperfused territory, the borders of which were defined in any given dog by the anatomy of the epicardial veins.

Possible mechanisms of distribution to ischemic myocardium. Two pressure gradients have been identified that might form the basis for selective flow to ischemic myocardium during retroinjection.

Systole. The systolic pressure gradient between the retroperfused vein and the coronary artery distal to its occlusion site would allow for selective flow to ischemic myocardium by reversal of the usual direction of the flow. Systole, however, is characterized by a high extravascular resistance to anterograde myocardial flow, probably a reflection of the high intramyocardial pressure during myocardial contraction (23–28). There is, however, a considerable decrease in subepicardial myocardial pressure in acutely ischemic myocardium despite a relatively unchanged left ventricular pressure (29,30). Thus, it seems possible that this venoarterial pressure gradient favors flow to the ischemic subepicardium. The relatively higher intramyocardial pressures of the normal myocardium (29,30) would further favor preferential flow to the ischemic zone, manifesting low intramyocardial pressures.

The territory of the occluded coronary artery would be the recipient of this flow. Because there is probably no drainage through arterioarterial collateral vessels against normal systemic arterial pressure, the compliance of the retrogradely filled arteries would determine the amount of flow. In this respect, the increase in pressure of the occluded coronary artery during retroinjection (Table 3) would be consistent with retrograde filling of a vascular tree with a limited compliance. However, even if this restrictive compliance were to prevent unidirectional flow sufficient to restore adequate oxygen delivery, oscillatory movement (10) of fluid into and out of an ischemic area could still be effective in delivering a drug.

Diastole. The diastolic pressure gradient is the driving force for flow from the epicardial vessels to the left ventricular chamber via thebesian vessels and intramyocardial sinusoids (6,10,12,31–36). Such flow was visualized during retroinjection in vivo in the echocardiographic study of Maurer et al. (12). Retroinjected fluid that leaves the thebesian veins during diastole to enter the left ventricular chamber is unavailable for retrodistribution and constitutes one of the shunt pathways to the systemic circulation. However, the part of the injectate that enters the thebesian veins and intramyocardial sinusoids during diastole might be pushed back to both the intramural and epicardial vascular beds by the passive pressure buildup in ischemic myocardium transmitted from the left ventricular chamber (37).

Although our data do not allow us to determine the relative importance of these two mechanisms in the selective flow distribution to the ischemic myocardium, our described pressure gradients developed during retroinjection outline the basic condition under which retrodistribution occurs. A

diastolic coronary venoarterial pressure gradient does not appear to be essential for selective distribution because four of five dogs showed no such gradient during retroinjection associated with selective staining of ischemic myocardium (Table 3). If present, a gradient of this sort certainly would contribute to selective delivery of the injectate to ischemic myocardium.

Effective "back pressure." Because our experiments did not yield quantitative data on retrograde flow, we cannot determine the effective "back pressure" (24–26,38,39) opposing retrograde flow. Conceivably, there is a wide range of back pressures, depending on the myocardial depth and the phase of the cardiac cycle. For example, during systole, different intramyocardial pressures at various depths of the myocardial wall might constitute an array of back pressures. In diastole, the left ventricular pressure might reflect only the back pressure for flow across capillaries draining into the left ventricle, with higher back pressures for flow draining into the occluded coronary artery (Fig. 4). The situation is further complicated by 1) the rhythmic changes in the capacity of the coronary arteries and veins, and 2) a phasic flow component created from the normal myocardium by virtue of its squeezing action on the coronary veins (8,26) within the retroperfused area.

Venovenous shunting in epicardial veins. When the site of coronary venous occlusion is the distal great cardiac vein, relatively large epicardial veins at the anterolateral or posterior aspect of the left ventricle (40) may shunt a considerable portion of the injectate to the right atrium, and thus diminish the buildup of pressure gradients. In dogs with extensive venovenous shunts, these two factors may well contribute to less effective dye delivery to ischemic sites. Direct measurement of the coronary venous pressure during retroinjection, as used in this study, appears to be an important step in the attempt to reach reproducible degrees of retroperfusion from the great cardiac vein (41).

Comparison with other studies. Our findings of selective staining of ischemic myocardium are in accord with the studies of Taira et al. (15), but they differ from other studies (10,12) in which various degrees of retrograde penetration into normal myocardium were reported. Apart from differences in the experimental protocol or the viscosity of the injectate, or both, the coronary venous pressure attained during retroinjection was not monitored in these studies. With the coronary venous pressure exceeding the systemic arterial pressure, even normal myocardium can conceivably be retroperfused. Furthermore, both studies (10,12) did not show retrograde delivery of the injectate to the capillary level of the normal myocardium. Retrograde injectate described in the normal myocardium could, thus, simply reflect retrograde filling of the larger epicardial and intramural veins.

Limitations of this study. Monastral blue dye is a nonquantitative marker for flow. On a qualitative basis, however, the differences in the staining of normal and ischemic myocardium were striking on both the macroscopic and the histologic levels. Despite these shortcomings, Monastral blue dye offers the advantage of allowing the localization of the injectate in relation to its vascular distribution. Because the ischemic and the retroperfused areas were not quantitatively measured, the degree to which the entire ischemic area was penetrated could not be assessed. Similarly, because of the qualitative nature of the dye distribution, we made no correlation between the intensity of myocardial staining and the magnitude of the pressure gradients developed during retroinjection. However, even given the same pressure gradients in different dogs, varying intensities of staining are to be expected owing to variable degrees of shunting through epicardial venovenous connections. This study was confined to acute ischemia; in the subacute and chronic phases of myocardial infarction, however, additional factors such as myocardial edema, formation of connective tissue and coronary venous thrombosis might affect myocardial staining.

Clinical implications. Initial clinical studies suggest that coronary venous retroperfusion could support the jeopardized myocardium during acute ischemia (42). It would then be appropriate when retrograde injection of a drug is considered in human patients to carefully evaluate the dependence of the retrograde distribution pattern on the myocardial perfusion pressure. With normal systemic blood pressure, much higher drug concentrations might be reached preferentially to an ischemic area than during systemic hypotension, a situation that is associated with more diffuse staining. Furthermore, because extensive epicardial venovenous connections have also been described in human subjects (43), a variable amount of the injectate during great cardiac vein retroinjection can be expected to be shunted directly to the right atrium, thus decreasing delivery of the injectate to ischemic sites.

In conclusion, great cardiac vein retroinjection provides a means to selectively deliver drugs to ischemic myocardium. This approach might prove to offer a valuable alternative in the management of acute ischemic syndromes when various substrates are contemplated to be delivered to hypoperfused ischemic myocardial sites.

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References

1. Meerbaum S, Lang T-W, Osher JV, et al. Diastolic retroperfusion of acutely ischemic myocardium. Am J Cardiol 1976;37:588–97.
2. Farcot JC, Meerbaum S, Lang T-W, Kaplan L, Corday E. Synchro-

nized retroperfusion of coronary veins for circulatory support of jeopardized ischemic myocardium. Am J Cardiol 1978;41:1191–201.

3. Berdeaux A, Farcot J-P, Bourdarias J-P, Barry M, Bardet J, Giudicelli J-F. Effects of diastolic synchronized retroperfusion on regional blood flow in experimental myocardial ischemia. Am J Cardiol 1981;47: 1033–40.
4. Smith GT, Geary GG, Blanchard W, McNamara JJ. Reduction in infarct size by synchronized selective coronary venous retroperfusion of arterialized blood. Am J Cardiol 1981;48:1064–70.
5. Meerbaum S, Haendchen RV, Corday E, et al. Hypothermic coronary venous phased retroperfusion: a closed chest treatment of acute regional myocardial ischemia. Circulation 1982;65:1435–45.
6. Geary GG, Smith GT, Suehiro GT, Zeman C, Siu B, McNamara JJ. Quantitative assessment of infarct size reduction by coronary venous retroperfusion in baboons. Am J Cardiol 1982;50:1424–30.
7. Meerbaum S, Lang T-W, Povzhitkov M, et al. Retrograde lysis of coronary artery thrombus by coronary venous streptokinase administration. J Am Coll Cardiol 1983;1:1262–7.
8. Mohl W, Glogar DH, Mayr H, et al. Reduction of infarct size by pressure-controlled intermittent coronary sinus occlusion. Am J Cardiol 1984;53:923–8.
9. Mohl W, Punzengruber C, Moser M, et al. Effects of pressure-controlled intermittent coronary sinus occlusion on regional ischemic myocardial function. J Am Coll Cardiol 1985;5:939–47.
10. Cibulski AA, Markov A, Lehan P, et al. Retrograde radioisotope myocardial perfusion pattern in dogs. Circulation 1974;50:159–66.
11. Menasche P, Kural S, Fauchet M, et al. Retrograde coronary sinus perfusion: a safe alternative for ensuring cardioplegic delivery in aortic valve surgery. Ann Thorac Surg 1982;34:647–57.
12. Maurer G, Punzengruber C, Haendchen RV, et al. Retrograde coronary venous contrast echocardiography: assessment of shunting and delineation of regional myocardium in the normal and ischemic heart. J Am Coll Cardiol 1984;4:577–86.
13. Karagueuzian HS, Ohta M, Drury JK, et al. Coronary venous retroinfusion of procainamide: a new approach for the management of spontaneous and inducible sustained ventricular tachycardia during myocardial infarction. J Am Coll Cardiol 1986;7:551–63.
14. Otsu F, Carew TE, Maroko PR. Myocardial concentration and antiarrhythmic effect of lidocaine administered via coronary veins (abstr). J Am Coll Cardiol 1985;5:467.
15. Taira Y, Kanaide H, Nakamura M. Coronary venous perfusion of the ischemic myocardium during acute coronary artery occlusion in isolated rat hearts. Circ Res 1985;56:666–75.
16. Meesmann M, Karagueuzian HS, Ino T, McCullen A, Mandel WJ, Peter T. Coronary venous retroinjection of procainamide has more pronounced effects on ischemic myocardium than the intravenous systemic injection (abstr). PACE 1986;9:310.
17. Karagueuzian HS, Fenoglio JJ Jr, Weiss MB, Wit AL. Protracted ventricular tachycardia induced by premature stimulation of the canine heart after coronary artery occlusion and reperfusion. Circ Res 1979;44: 833–46.
18. Lowe JE, Reimer KA, Jennings RB. Experimental infarct size as a function of the amount of myocardium at risk. Am J Pathol 1978;90: 363–80.
19. Jugdutt BI, Hutchins GM, Bulkley BH, Becker LC. Myocardial infarction in the conscious dog: three-dimensional mapping of infarct, collateral flow and region at risk. Circulation 1979;60:1141–50.
20. Hearse DJ, Opie LH, Katzeff IE, et al. Characterization of the "border zone" in acute regional ischemia in the dog. Am J Cardiol 1977;40: 716–26.
21. Hearse DJ, Yellon DM. The "border zone" in evolving myocardial infarction: controversy or confusion? Am J Cardiol 1981;47:1321–34.
22. Godfrey K. Simple linear regression in medical research. N Engl J Med 1985;313:1629–36.
23. Sabiston DC, Gregg DE. Effect of cardiac contraction on coronary blood flow. Circulation 1957;15:14–20.
24. Downey JM, Kirk ES. Distribution of coronary blood flow across the canine heart wall during systole. Circ Res 1974;34:251–7.
25. Downey JM, Kirk ES. Inhibition of coronary blood flow by a vascular waterfall mechanism. Circ Res 1975;36:753–60.
26. Feigl EO. Coronary physiology. Physiol Rev 1983;63:1–176.
27. Brandi G, McGregor M. Intramural pressure in the left ventricle of the dog. Cardiovasc Res 1969;3:472–5.
28. Stein PD, Marzilli M, Sabbah HN, Lee T. Systolic and diastolic pressure gradients within the left ventricular wall. Am J Physiol 1980;238: H625–30.
29. Baird RJ, Ameli FM. The changes in intramyocardial pressure produced by acute ischemia. J Thorac Cardiovasc Surg 1971;62:87–94.
30. Sabbah HN, Stein PD. Effect of acute regional ischemia on pressure in the subepicardium and subendocardium. Am J Physiol 1982;242: H240–4.
31. Wearn JT. The role of the thebesian vessels in the circulation of the heart. J Exp Med 1927;47:293–315.
32. Lendrum B, Kondo B, Katz LN. The role of thebesian drainage in the dynamics of coronary flow. Am J Physiol 1945;143:243–6.
33. Scharf SM, Bromberger-Barnea B, Permutt S. Distribution of coronary venous flow. J Appl Physiol 1971;30:657–62.
34. Lolley DM, Hewitt RL. Myocardial distribution of asanguinous solutions retroperfused under low pressure through the coronary sinus. J Cardiovasc Surg 1980;21:287–94.
35. Faxon DP, Jakobs AK, Kellett MA, McSweeney SM, Coats WD, Ryan TJ. Coronary sinus occlusion pressure and its relation to intracardiac pressure. Am J Cardiol 1985;56:457–60.
36. Gould SE. Pathology of the Heart and Blood Vessels. 3rd ed. Springfield, IL: Charles C Thomas, 1983:111.
37. Snyder R, Downey JM, Kirk ES. The active and passive components of extravascular coronary resistance. Cardiovasc Res 1975;9:161–6.
38. Permutt S, Bromberger-Barnea B, Bane HN. Alveolar pressure, pulmonary venous pressure, and the vascular waterfall. Medicina Thoracalif 1962;19:239–60.
39. Klocke FJ, Mates RE, Canty JM, Ellis AK. Coronary pressure-flow relationships. Controversial issues and probable implications. Circ Res 1985;56:310–23.
40. Eliskova M, Eliska O. Subepicardial veins of the dog's heart and their anastomoses. Acta U Carol [Med] 1966;12:21–30.
41. Meerbaum S. The promise and limitations of coronary venous retroperfusion: lessons from the past and new directions. In: Mohl W, Faxon D, Wolner E, eds. Progress in Coronary Sinus Interventions. CSI—A New Approach to Interventional Cardiology. Darmstadt: Steinkopff Verlag, 1986:40.
42. Corday E, Meerbaum S, Drury JK. The coronary sinus: an alternate channel for administration of arterial blood and pharmacologic agents for protection and treatment of acute cardiac ischemia. J Am Coll Cardiol 1986;7:711–4.
43. Gensini GG, DiGiorgi S, Coskun O, Palacio A, Kelly AE. Anatomy of the coronary circulation in living man. Coronary venography. Circulation 1965;31:778–84.