JACC Vol. 18, No. 2
August 1991:603–12

SEMINAR ON CORONARY VENOUS DELIVERY SYSTEMS FOR SUPPORT AND SALVAGE OF JEOPARDIZED ISCHEMIC MYOCARDIUM—II*

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Pharmacokinetic Analysis of Coronary Venous Retroinfusion: A Comparison With Anterograde Coronary Artery Drug Administration Using Metoprolol as a Tracer

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Plasma and myocardial tissue concentrations of metoprolol were studied in ischemic and nonischemic areas of 22 pigs after 90 (n = 19) and 16 (n = 3) min of left anterior descending coronary artery occlusion. Group A (n = 6) received simultaneous intravenous metoprolol (0.2 mg/kg body weight) and tritium-labeled (^{3}H)-metoprolol (0.2 mg/kg) retrogradely into the coronary vein. In group B (n = 5), metoprolol and ^{3}H-metoprolol were administered in the same way, but at half the volume to study the influence of derived coronary venous pressure on the myocardial concentration of drug. In group C (n = 3), metoprolol was given retrogradely and saline solution was infused into the left anterior descending artery before induced death to wash out metoprolol from the coronary veins. To rule out a possible influence of the development of myocardial necrosis on drug distribution, metoprolol was retroinfused after 1 min of arterial occlusion in three pigs (group D). In group E (n = 5), metoprolol (0.2 mg/kg) was infused anterogradely into the left anterior descending artery.

Peak plasma concentration was significantly higher after intravenous infusion of metoprolol (1,188 ± 503 nmol/liter) than after coronary venous infusion (417 ± 155 nmol/liter; $p < 0.001$). In groups A and B, the nonischemic myocardial concentration of metoprolol was 250 to 300 pmol/g, whether the drug was infused intravenously or into the coronary vein. Coronary venous retroinfusion, however, resulted in a substantial accumulation of metoprolol in the ischemic myocardium. In group A pigs, subendocardial myocardial concentration was 16,800 ± 7,774, midmyocardial 39,590 ± 18,043 and subepicardial 57,143 ± 29,030 pmol/g (mean ± SE). The ischemic myocardial concentration in pigs from group B was somewhat less pronounced, probably secondary to a lower coronary venous pressure (15 ± 3 mm Hg) with the lower volume of infusion (6.1 ± 0.3 ml) in group B compared with 32 ± 5 mm Hg with a 14 ± 1 ml infusion in group A. Coronary artery anterograde administration resulted in myocardial ischemic and nonischemic zone drug concentrations similar to those observed after retroinfusion into the coronary vein. With both modes of administration, there was a transmyocardial gradient from a somewhat lower drug concentration in the subendocardium, toward an increasing level in the midmyocardium, to the highest concentration in the subepicardial zone of the ischemic myocardium.

Coronary venous retroinfusion resulted in pronounced drug accumulation in the ischemic myocardium. The derived coronary venous pressure during infusion influenced the concentration of drug. The ischemic myocardial levels and distribution pattern were similar to those seen with coronary artery anterograde infusion. The high tissue levels of drug were not affected by saline solution flush. These findings suggest that coronary venous retroinfusion may deliver drugs to a microvascular level of ischemic myocardium, with a distribution similar to that achieved after direct arterial infusion.

(J Am Coll Cardiol 1991;18:603–12)

*Part I of this Seminar appeared in the July issue of the Journal (J Am Coll Cardiol 1991;18:253–302).

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Manuscript received July 25, 1990; revised manuscript received December 17, 1990, accepted January 10, 1991.

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0735-1097/91/$3.50

After experiments with retroperfusion of arterial blood into the coronary veins of freshly extirpated cat hearts, Pratt (1) in 1893 concluded that "the nutrition of the mammalian heart is not completely dependent on the coronary arteries." In 1948, Beck et al. (2) introduced the concept of coronary sinus perfusion into clinical medicine with the Beck II surgical procedure, whereby blood was shunted from the aorta to the coronary sinus. Despite short-term improvement of cardiac function in patients with ischemic heart disease, this technique was abandoned because of late complications mainly secondary to myocardial edema and hemorrhage. Interest in coronary venous interventions in 1976 was renewed with the introduction of synchronized coronary venous retroperfusion by Meerbaum et al. (3). Originally, coronary venous interventions were intended for the retrograde delivery of arterial blood for temporary support of acutely ischemic myocardium (4,5). However, it was soon evident that the coronary veins also provided a route for the administration of pharmacologic agents (6,7). Thus, coronary venous retroinfusion refers to a technique for the coronary venous delivery of pharmacologic agents to the myocardium. This application may be used together with retroperfusion or independently (4,5).

Recent experimental evidence (6,8,9) demonstrates benefits from the retroinfusion of various pharmacologic agents such as streptokinase, procainamide, diltiazem and oxygen free radical scavengers. Consequently, coronary venous retroinfusion may have future important clinical potential. There is, however, only scattered and limited information on pharmacokinetics after retroinfusion. In a recent pilot investigation we (10) found that coronary venous retroinfusion of the beta-adrenergic blocking agent metoprolol resulted in a pronounced drug accumulation in the ischemic myocardium of pigs after coronary artery ligation and that this drug would be suitable as a tracer in a more extensive pharmacokinetic study of coronary venous retroinfusion of drugs.

The aim of the present investigation was to compare systemic intravenous and retrograde coronary venous administration of drugs in terms of the distribution in plasma and ischemic and nonischemic myocardium. Furthermore, we wanted to test the hypothesis that delivery of drug into the coronary venous system may result in an accumulation of drug in the ischemic myocardium similar to that achieved by anterograde infusion into the coronary arteries.

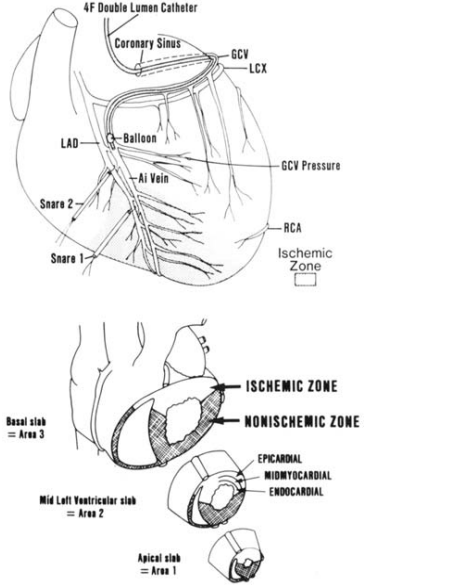


Figure 1. Schematic illustration of the experimental porcine preparation, demonstrating the position of the snares around the left anterior descending (LAD) coronary artery and the position of the coronary sinus catheter. **Stippled area** outlines the ischemic zone. Snare 1 was used for partial left anterior descending artery occlusion; the complete occlusion was applied by snare 2. This protocol was used in groups A, B, C and E. In pigs in group C, complete left anterior descending artery occlusion was directly applied at the site of snare 2. Pigs in group C and E also had an 18 gauge Angiocath inserted into left anterior descending artery at the site of snare 2. **The lower illustration** shows the apical, mid-left ventricular and basal slabs for study of ischemic and nonischemic areas. Ai vein = anterior cardiac vein; GCV = great cardiac vein; LCX = left circumflex coronary artery; RCA = right coronary artery.

Methods

Animal preparation. Twenty-two male or female farm pigs weighing 27 to 45 kg (mean ± SE 34 ± 1) were included. The pigs were premedicated with intramuscular injections of ketamine hydrochloride (20 mg/kg body weight) and atropine (0.1 mg/kg). Anesthesia was induced by an intravenous injection of sodium pentobarbital (20 to 30 mg/kg) and maintained by a continuous infusion of this agent (2 to 6 mg/kg per h). A tracheotomy was performed and the pigs were ventilated mechanically by a Harvard respirator. Respiratory rate and tidal volume were adjusted to keep the pH and partial pressure of carbon dioxide (Pco_2) within the normal range. Body temperature was kept between 37.5° and 38°C.

Two 4F catheters introduced through the femoral veins were positioned in the inferior vena cava for the administration of drugs and fluids and withdrawal of blood specimens (Fig. 1). A 7F catheter positioned in the aortic arch through the left carotid artery was used to measure aortic blood pressure by means of a Statham P23Db transducer. An 8F

Table 1. Pertinent Data From the Experimental Procedure in the Five Groups of Pigs

Group	Drug	Site of Infusion	Dose (mg/kg)	Drug Concentration (mg/ml)	Remarks
A (n = 6)	^{3}H-metoprolol	Coronary vein	0.2	0.5	Infusion after 30 min of complete LAD occlusion; induced death 60 min later
	Metoprolol	Right atrium	0.2	0.5	
B (n = 5)	^{3}H-metoprolol	Coronary vein	0.2	1.0	As in group A
	Metoprolol	Right atrium	0.2	1.0	
C (n = 3)	Metoprolol	Coronary vein	0.2	0.5	As in group A, but with LAD flush (10 ml of saline solution) from the site of occlusion before induced death
D (n = 3)	Metoprolol	Coronary vein	0.2	0.5	Infusion after 1 min of complete LAD occlusion; induced death 15 min later
E (n = 5)	Metoprolol	LAD	0.2	0.5	Infusion after 30 min of complete LAD occlusion; induced death 60 min later

LAD = left anterior descending coronary artery.

MIKRO-TIP catheter transducer (Millar Instruments) inserted through the right carotid artery was positioned in the left ventricle to record pressure. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic derivation. In pigs that received coronary venous retroinfusion, an 8F catheter was inserted through the left external jugular vein and advanced into the coronary sinus orifice.

Access to the heart was achieved by a left thoracotomy in the fifth intercostal space and the pericardium was opened. In all pigs except those belonging to group D (see later), two silk ligatures were passed around the left anterior descending coronary artery. One ligature was placed approximately 1 cm below the first major diagonal branch and the second approximately 1.5 cm more distally. Pigs in group D received only the proximal ligature. All pigs except those in group E (see later) had a 4F double lumen balloon catheter inserted through the previously positioned coronary sinus introducer. The balloon of the double lumen catheter was positioned in the anterior interventricular vein just above the site of the most proximal left anterior descending artery snare. The center lumen of the catheter was used for the infusion of metoprolol and the other for balloon inflation to occlude the cardiac vein during drug delivery. A 22 gauge intravenous catheter (Angiocath) was introduced into a branch of the anterior interventricular vein distal to the site of occlusion for pressure monitoring (Fig. 1). All pigs received heparin (3,000 IU/kg intravenously) after instrumentation. Lead II of the electrocardiogram (ECG) and all pressures were continuously monitored on an Electronics for Medicine physiologic recorder.

Experimental procedure (Table 1). After instrumentation and before left anterior descending artery occlusion, control hemodynamic recordings were obtained in all pigs. The pigs were assigned to one of five groups: group A (n = 6), group B (n = 5), group C (n = 3), group D (n = 3) and group E (n = 5). The most important differences among these groups are summarized in Table 1. In pigs belonging to groups A, B, C and E, the distal silk suture was tied around the left anterior descending artery and a 20 gauge hypodermic needle. This needle was immediately removed, leaving the vessel partly occluded during 30 min, after which the artery was completely ligated at the proximal site. This sequential ligation procedure was done to minimize the risk of ventricular fibrillation frequently observed after acute one-stage coronary artery ligation in pigs (11). After 30 min of complete ischemia, pigs in groups A and B received metoprolol simultaneously infused into the coronary vein (0.2 mg/kg of tritium-labeled [^{3}H]-metoprolol) and intravenously (0.2 mg/kg of unlabeled metoprolol).

Immediately before the onset of retroinfusion, the balloon on the catheter in the anterior interventricular vein was inflated to prevent drug regurgitation. The balloon was kept inflated during the 5 min period of infusion and for an additional 2 min after completion of the infusion. By visual inspection, it was ascertained that the inflated balloon occluded the coronary vein. The only difference between groups A and B was that metoprolol was given in a concentration of 0.5 mg/ml in group A and 1 mg/ml in group B. Accordingly, the infused volume was 14 ± 1 ml (mean ± SE) in group A and 6.1 ± 0.3 ml in group B. The pigs in groups A and B were killed 60 min after the start of metoprolol infusion.

Pigs in group C were similar to those in groups A and B, but received only unlabeled metoprolol in the coronary vein. In these pigs, saline solution (10 ml) was injected during 1 min into an 18 gauge catheter (Angiocath) inserted in the left anterior descending artery at the time and site of proximal occlusion. Thus, the proximal coronary artery snare was tied around this catheter.

In group D, the left anterior descending artery was occluded at the proximal site without prior distal partial occlusion and unlabeled metoprolol was infused into the coronary vein 1 min after occlusion in a manner similar to that previously described. These pigs were killed 15 min after metoprolol infusion.

In group E, the pigs were handled as in groups A and B,

with the exception that infusion of unlabeled metoprolol was made into the left anterior descending artery through a catheter introduced as in group C.

To outline ischemic and nonischemic myocardium, 20 ml of 10% monastral blue dye was injected into the left atrium at the end of the observation period in all pigs, after which the animals were killed by injection of potassium chloride.

Recordings and specimens. Hemodynamic recordings were made before coronary artery occlusion (control), before (0) and at 5, 15, 30 and 60 min after the start of metoprolol infusion. Blood for the analysis of plasma metoprolol concentrations was obtained at 5, 10, 15, 20, 30, 45 and 60 min after the start of the infusion. After extirpation, the heart was cut into apical, mid-ventricular and basal slabs (Fig. 1). Ischemic myocardial tissue was derived from each of these slabs and nonischemic myocardium was taken from the mid-ventricular slab. Myocardial tissue from each site was separated into subendocardial, mid-myocardial and subepicardial portions. Plasma and tissue specimens were kept at −20°C until analyzed.

Analysis of metoprolol, ^{3}H-metoprolol and radioactive metabolites. The concentrations of metoprolol in tissue homogenates and in plasma originating from the intravenous dose were calculated from the differences between the metoprolol concentrations determined by gas chromatography mass spectrometry (12,13) and the concentration of ^{3}H-metoprolol in the same samples. The ^{3}H-metoprolol concentration was determined by liquid scintillation counting after separation from its metabolites by column liquid chromatography (14). Eluted fractions with a retention time corresponding to the ultraviolet signal of the internal standard of cold metoprolol were collected in scintillation liquid (Ready Safe, Beckman Instruments) and the radioactivity was measured with a Beckman 3800 liquid scintillation counter. A validation of the metoprolol assay has been performed; in the present set of experiments, considering the sample size, metoprolol levels >10 pmol/g could be determined with a relative SD of <10% (12,13). The assay of ^{3}H-metoprolol was tested under the conditions of the present study: ^{3}H-metoprolol could be quantified with an SD of 2.8% to 3.8% (n = 10) in a concentration range of 15 to 400 pmol/g.

Statistics. Statistical methods included analysis of variance (ANOVA) with either one grouping factor and one or two repeated measures factors. Significant ANOVA effects ($p < 0.05$) were assessed by Tukey's pairwise multiple comparison procedure (15,16). Within-subject comparisons were analyzed with Friedman's analysis of variance using a ranking procedure (17). Significant results from the Friedman test were evaluated by the nonparametric analog of Tukey's multiple comparison procedure. Between-subject comparisons were conducted for each level of a repeated measures factor using a ranking procedure (17). Significant results were determined by the nonparametric analog of Tukey's multiple comparison procedure. All data are presented as mean values ± SE. A p level < 0.05 was considered statistically significant.

Results

Hemodynamics (Tables 2 and 3). There were no differences among groups A to E with respect to hemodynamic variables at control study (before left anterior descending artery occlusion) or directly before drug infusion. The infusion of metoprolol did not significantly influence heart rate, systemic blood pressure or left ventricular pressure; however, metoprolol infusion resulted in a reduction in left ventricular dP/dt 5 and 15 min after the start of the injection (Table 2). In group A, occlusion of the coronary vein and coronary venous retroinfusion caused a significant increase in mean coronary venous pressure peaking at the end of the infusion (Table 3). The pressure increase in group B pigs receiving the low volume infusion was less pronounced (p = NS). At the end of injection, peak coronary venous pressure was 43 ± 5 mm Hg in group A, 30 ± 6 mm Hg in group B, 47 ± 2 mm Hg in group C and 59 ± 5 mm Hg in group D. The highest peak coronary venous pressure was 66 mm Hg in one pig in group D.

Plasma concentration (Fig. 2). Plasma metoprolol concentrations after intravenous and coronary venous retroinfusion in group A are presented in Figure 2. The results obtained in the other groups were similar and are therefore not reported. Mean peak plasma concentration obtained from intravenous infusion was 1,188 ± 503 nmol/liter (unlabeled metoprolol) compared with 417 ± 155 nmol/liter (^{3}H-metoprolol) with coronary venous retroinfusion ($p < 0.001$). Plasma levels of the retroinfused ^{3}H-metoprolol remained significantly lower throughout the 60 min observation period ($p < 0.05$).

Myocardial concentration (Fig. 3 and 4). Average ischemic and nonischemic myocardial tissue drug concentrations in the subendocardial, mid-myocardial and subepicardial zones after intravenous injection (unlabeled metoprolol) and coronary venous retroinfusion (^{3}H-metoprolol) in group A are shown in Figure 3. Whether given intravenously or retrogradely, nonischemic myocardial tissue concentrations were approximately 260 pmol/g. Ischemic zone concentration after coronary venous retroinfusion was substantially higher, with values of 16,800 ± 7,774 pmol/g in the subendocardium, 39,590 ± 18,043 pmol/g in the mid-myocardium and 57,143 ± 29,030 pmol/g in the subepicardium. The difference between nonischemic and ischemic myocardial tissue concentrations was statistically significant ($p < 0.05$) as was the transmyocardial gradient, with lowest levels in the subendocardium and highest levels in the subepicardium ($p < 0.05$). There was very little unlabeled metoprolol (administered intravenously) in the ischemic and even less in the nonischemic myocardium. Because the concentration was within the error of the method of analysis (separating unlabeled from ^{3}H-metoprolol), it could not be defined in detail. There was a trend toward higher myocardial metoprolol concentrations in myocardial slabs from the apical toward the basal parts of the left ventricle, reaching statis-

Table 2. Hemodynamic Variables Before Left Anterior Descending Coronary Artery Occlusion and at Various Times After Metoprolol Infusion

Variable	Time After Metoprolol (min)					
	Control	0	5	15	30	60
Heart rate (beats/min)						
Group A	116 ± 7	107 ± 7	102 ± 6	103 ± 7	104 ± 7	106 ± 8
Group B	104 ± 5	102 ± 5	101 ± 5	100 ± 4	99 ± 4	101 ± 5
Group C	127 ± 6	133 ± 13	126 ± 10	125 ± 8	125 ± 9	125 ± 10
Group D	—	123 ± 4	110 ± 4	105 ± 2	—	—
Group E	113 ± 6	103 ± 9	105 ± 8	101 ± 7	101 ± 7	100 ± 7
Mean arterial pressure (mm Hg)						
Group A	88 ± 6	87 ± 6	86 ± 7	87 ± 7	88 ± 8	89 ± 10
Group B	97 ± 6	105 ± 6	104 ± 8	117 ± 10	117 ± 10	120 ± 11
Group C	86 ± 3	89 ± 6	84 ± 5	90 ± 6	91 ± 6	93 ± 6
Group D	—	94 ± 5	87 ± 4	86 ± 5	—	—
Group E	101 ± 9	93 ± 8	89 ± 7	90 ± 7	91 ± 6	93 ± 7
LV systolic pressure (mm Hg)						
Group A	101 ± 6	102 ± 5	102 ± 5	103 ± 6	104 ± 7	113 ± 6
Group B	115 ± 5	123 ± 7	130 ± 8	135 ± 10	134 ± 10	138 ± 10
Group C	99 ± 5	104 ± 8	98 ± 7	103 ± 7	105 ± 6	106 ± 7
Group D	—	110 ± 1	106 ± 6	101 ± 7	—	—
Group E	119 ± 9	114 ± 8	105 ± 6	109 ± 9	110 ± 8	113 ± 8
LV diastolic pressure						
Group A	9 ± 1	12 ± 1	12 ± 1	11 ± 1	11 ± 1	10 ± 1
Group B	9 ± 2	10 ± 2	11 ± 2	9 ± 2	9 ± 1	9 ± 1
Group C	10 ± 1	14 ± 3	13 ± 1	14 ± 1	14 ± 1	13 ± 1
Group D	—	9 ± 1	13 ± 2	12 ± 2	—	—
Group E	11 ± 1	13 ± 1	13 ± 2	12 ± 1	12 ± 1	12 ± 2
LV dP/dt (mm Hg × s^{-1})						
Group A	1,298 ± 116	1,183 ± 102	1,049 ± 86*	1,111 ± 72*	1,121 ± 92	1,231 ± 39
Group B	1,279 ± 153	1,466 ± 205	1,133 ± 125*	1,269 ± 156*	1,305 ± 148	1,292 ± 111
Group C	1,478 ± 617	1,096 ± 213	1,013 ± 141*	933 ± 102*	933 ± 107	1,014 ± 78
Group D	—	1,367 ± 256	1,012 ± 119*	993 ± 118*	—	—
Group E	1,472 ± 195	1,562 ± 166	1,168 ± 128*	1,235 ± 174*	1,260 ± 126	1,240 ± 142

*$p < 0.05$ versus 0 min after metoprolol. Data are mean values ± SE for the different groups. dP/dt = first derivative of left ventricular (LV) pressure.

tical significance ($p < 0.05$) for the subendocardial and mid-myocardial zones (Fig. 4).

Effect of the various modes of administration on ischemic myocardial metoprolol concentration (Fig. 5 and 6, Table 4). With use of group A as a standard, there was a trend toward lower myocardial tissue concentrations after the low volume infusion (group B) (Fig. 5). The coronary artery saline solution flush before induced death (group C) did not have any important influence on the myocardial tissue concentrations. Retroinfusion of drug 1 min after complete occlusion of the left anterior descending coronary artery (group D) tended to give a somewhat higher myocardial concentration than when the drug was given 30 min after occlusion. Anterograde administration of drug through the left anterior descending artery (group E) and coronary venous retroinfusion (group A) resulted in comparable myocardial tissue concentrations. Individual myocardial concentrations did, however, show a considerable individual variability (Table 4). The ischemic myocardial concentration of drug was related to the mean coronary venous pressure at the end of infusion. The correlation for the subendocardial, mid-myocardial and subepicardial areas was 0.8851, 0.8143 and 0.8160, respectively ($p < 0.05$). The relation is presented in Figure 6 derived from all 14 pigs in groups A, B and C that underwent the same coronary artery occlusion protocol.

Discussion

Previous studies. To date, only limited information is available on myocardial tissue drug concentration after coronary venous retroinfusion. Karagueuzian et al. (8) studied the efficacy of retrograde delivery of procainamide for the management of ventricular tachycardia in dogs with permanent coronary occlusions. Although not reported in detail, myocardial procainamide concentration was 9 to 100 times higher in the ischemic left ventricular wall after retroinfusion than after intravenous administration. In a pilot study (10), we recently demonstrated that coronary venous retroinfusion of metoprolol resulted in substantial accumulation in ischemic myocardium, with average myocardial

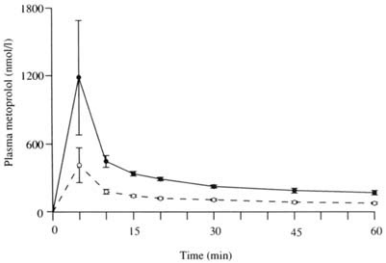
Table 3. Mean Coronary Venous Pressure (in mm Hg) Before and at Various Times After Metoprolol Infusion

Group and Pig No.	Time After Metoprolol (min)					
	Control	0	5	15	30	60
A1	17	13	44	13	12	10
A2	10	6	17	4	6	5
A3	13	13	40	30	20	12
A4	13	14	44	11	20	19
A5	23	9	23	14	16	10
A6	3	2	22	1	1	2
Mean	13	10	32	12	13	10
SE	3	2	5*	4	3	2
B1	20	16	16	14	12	10
B2	10	9	15	8	8	10
B3	10	7	9	5	4	4
B4	10	5	12	2	2	2
B5	10	8	25	4	4	2
Mean	12	9	15	7	6	6
SE	2	2	3	2	2	2
C1	20	12	32	6	5	6
C2	9	10	31	13	10	10
C3	10	9	25	7	7	6
Mean	13	10	29	8	7	7
SE	4	1	2	1	1	1
D1	—	11	43	14	—	—
D2	—	23	35	25	—	—
D3	—	17	45	12	—	—
Mean	—	17	41	17	—	—
SE	—	3	3	4	—	—

*$p < 0.001$ versus time 0.

concentrations much higher in ischemic compared with nonischemic myocardium. Accordingly, the present study provides the first extensive pharmacokinetic data supporting the concept that coronary venous retroinfusion may deliver pharmacologic agents to ischemic myocardium in a highly specific way, much more effective than systemic intravenous

Figure 2. Plasma metoprolol (mean value ± SE) after administration of 0.2 mg/kg administered intravenously (closed circles, unlabeled metoprolol) and retrogradely (open circles, ^{3}H-metoprolol) into the coronary vein. Data are derived from group A pigs.



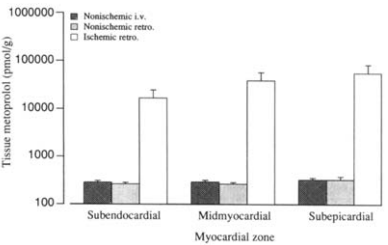


Figure 3. Myocardial tissue metoprolol (mean value ± SE) after administration of 0.2 mg/kg intravenously (i.v.) (unlabeled metoprolol) and retrogradely (retro.) into the coronary vein (^{3}H-metoprolol) of pigs.

administration. The technique with tritium-labeled (^{3}H) and unlabeled metoprolol permitted the pigs to be used as their own controls, ruling out uncertainties introduced by the use

Figure 4. Myocardial metoprolol in different ischemic areas from apex toward the base of the left ventricle (LV) after administration of 0.2 mg/kg. **A**, Data derived from group A pigs (coronary venous retroinfusion). **B**, Data derived from group E pigs (infusion anterogradely in left anterior descending coronary artery).

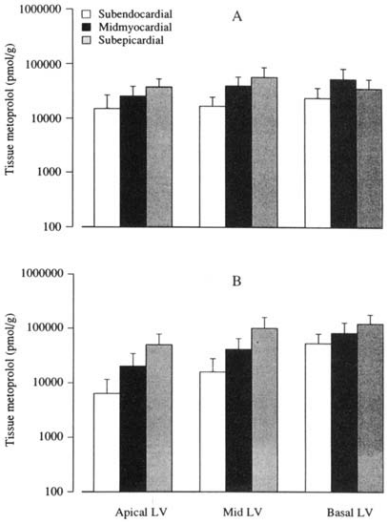


Table 4. Myocardial Concentration of Metoprolol (in pmol/g tissue) After Coronary Venous Retroinfusion

Group and Pig No.	Nonischemic			Ischemic		
	Endo	Mid	Epi	Endo	Mid	Epi
A1	305	297	458	22,230	85,000	102,000
A2	198	187	169	85	116	519
A3	296	334	503	42,280	99,000	181,000
A4	292	328	322	35,100	46,000	36,600
A5	277	291	244	566	2,960	3,907
A6	219	229	301	621	4,462	18,830
Mean	265	269	332	16,800	39,590	57,143
SE	18	20	51	7,774	18,043	29,030
B1	205	233	257	83	60	137
B2	139	135	129	51	58	122
B3	229	267	260	64	—	221
B4	241	235	291	826	3,623	3,615
B5	338	340	369	15,300	63,000	65,000
Mean	248	242	261	3,281	16,688	13,819
SE	35	33	39	3,028	15,460	12,813
C1	330	343	336	2,030	8,900	121,000
C2	291	300	313	7,100	58,099	53,000
C3	359	336	380	9,980	31,100	59,000
Mean	327	326	343	6,343	32,667	77,667
SE	20	13	20	2,303	14,196	21,736
D1	790	1,960	3,470	93,000	247,000	321,000
D2	1,320	1,590	1,700	31,400	59,500	183,400
D3	1,410	1,300	1,510	1,500	2,950	18,700
Mean	1,173	1,617	2,227	41,967	103,150	174,367
SE	193	191	6,4	26,957	73,754	87,383
E1	402	414	484	257	176	339
E2	234	254	298	4,160	18,100	7,400
E3	282	246	410	4,030	5,700	5,800
E4	496	930	540	8,600	52,000	235,000
E5	670	530	494	63,000	122,000	265,000
Mean	417	475	445	16,009	41,595	102,708
SE	78	126	42	11,832	24,328	60,330

Endo = endocardium; Epi = epicardium; Mid = mid-myocardium

of different animals for intravenous versus coronary venous administration.

Metoprolol myocardial concentrations: mechanisms of delivery. In the presence of ischemia, a drug with a large degree of lipid solubility will penetrate better into ischemic myocardium than will drugs without it (18,19). Metoprolol has a relatively high level of lipid solubility and accordingly has favorable pharmacokinetic properties for intravenous

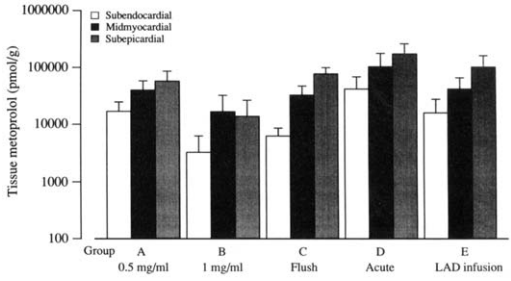


Figure 5. Ischemic myocardial metoprolol distribution after infusion of 0.2 mg/kg in the five groups of pigs: group A = "high" infusion volume; group B = "low" infusion volume; group C = "high" infusion volume + saline solution flush through the left anterior descending artery; group D = "high" infusion volume directly after coronary artery ligation; group E = "high" infusion volume anterogradely into the left anterior descending artery (LAD).

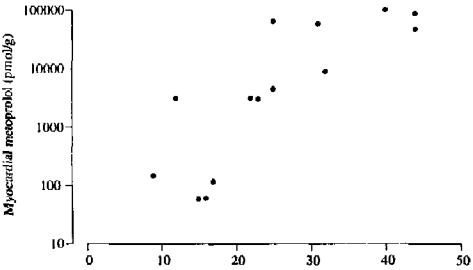


Figure 6. Relation between the mean coronary venous pressure (x axis [mm Hg]) at the end of coronary venous retroinfusion of 0.2 mg/kg of metoprolol and the mid-myocardial ischemic tissue concentration of metoprolol (y axis) in the 14 pigs in groups A, B and C.

administration. Nevertheless, intravenous metoprolol penetrated the ischemic zone poorly. Retroinfusion of labeled metoprolol demonstrated a high accumulation of the drug in the ischemic myocardium. In nonischemic areas, the amount of labeled drug was similar to the concentration achieved by intravenous infusion of unlabeled drug. Presumably, the labeled drug reached nonischemic myocardium by way of the systemic circulation after drug admixture resulting from veno-venous shunts and thebesian vein drainage. The accumulation of labeled metoprolol in ischemic myocardium is the probable reason for the lower plasma concentration after coronary venous administration.

Several mechanisms may contribute to the specific drug delivery to the ischemic zones and the low concentrations in the nonischemic areas. While being administered into the coronary vein, the drug would obviously be distributed primarily within the anatomic region drained by the vein of retroinfusion. The drug will have easier access to areas in which capillary perfusion pressure is low. Finally, without any anterograde blood flow through the ischemic area, the drug may accumulate at a microvascular level without subsequent washout.

Hemodynamic effects. In the present study, there were only minor hemodynamic effects despite the very high metoprolol concentration in the ischemic myocardium. However, this area of the heart is nonfunctioning and drug accumulation in the nonischemic normally functioning myocardium was not particularly high, thereby limiting a possible negative inotropic effect. It is recognized that in the experimental model used, pigs anesthetized with ketamine followed by pentobarbital, there are only minor effects on heart rate after treatment with a beta-adrenergic blocker. This has been documented not only for metoprolol (10), but also for propranolol (20). Adequate beta-blockade was verified in these studies by plasma concentration measurements and isoproterenol infusion, respectively. Therefore, further testing in animal models better designed for a thorough study of hemodynamic consequences is necessary.

Coronary venous retroperfusion versus anterograde coronary artery infusion. The comparison between coronary venous retroinfusion (group A) and anterograde coronary artery administration (group E) of drug revealed that the accumulation of drug in ischemic myocardium was of a similar magnitude and distribution. Comparisons between anterograde and retrograde delivery of drugs to the myocardium have not previously been presented. Thus, this observation represents new and potentially important information. Both modes of administration resulted in a transmyocardial gradient with lower concentrations in the subendocardial than in the subepicardial zones. It was also of interest that drug distribution was similar in the different myocardial slabs from apex toward the base.

Transmyocardial gradient of metoprolol distribution. There may be several causes of a transmyocardial gradient. One possibility is trapping of concentrated drug in subepicardial veins. However, such a mechanism is not likely considering the results in pigs in which an anterograde saline solution flush was performed before death was induced. These pigs (group C) had myocardial concentrations similar to those in pigs that did not receive a saline solution flush. The result in this group indicates that drug infused through the coronary veins distributes into the interstitial tissue fluid rather than in the veins, venules and capillaries.

Evolution of myocardial injury after coronary artery ligation propagates as a wave front from subendocardial toward subepicardial regions. In pigs, 30 min of partial and 30 min of complete coronary artery occlusion are sufficient to cause severe myocardial damage (21–23). It may be assumed that this injury would be most pronounced in the subendocardial layers and that a no reflow phenomenon may result in redistribution toward the less injured subepicardial myocardium. However, retroinfusion 1 min after left anterior descending artery occlusion (group D) resulted in myocardial concentration gradients similar to those recorded after 60 min of occlusion. For procainamide, cell viability is essential for drug binding because much lower drug levels

are found in necrotic compared with normal or ischemic but nonnecrotic myocardium (24). However, the similarity in metoprolol distribution after 1 and 90 min of ischemia suggests that variable cell binding does not explain the present results. One obvious reason is that the transmyocardial gradient results from the venous and capillary anatomic distribution, explaining the similarity in results with anterograde and retrograde administration. Another possible explanation is that intramural pressure propagation from the left ventricular cavity makes the subendocardial myocardium more difficult to penetrate. The relation between mean coronary venous pressure and myocardial concentration of drug gives some support to this latter explanation. A third possibility may be more rapid drainage of metoprolol from the subendocardium into the blood of the ventricular cavity than from the mid-myocardial and subepicardial zones.

Role of coronary venous pressure. To promote local absorption of drug in the ischemic myocardium, the drug was prevented from regurgitating by inflating a balloon at the tip of a coronary venous catheter. It is mandatory to monitor coronary venous pressure continuously during the infusion (25). As a general guideline, the peak pressure should never be >60 mm Hg or the mean pressure >40 mm Hg. In the present series, one pig had a peak pressure of 66 mm Hg for a short period of time and four pigs had a mean coronary venous pressure >40 mm Hg. There were no signs of coronary venous damage in any of these animals; however, the duration of the infusion was short. The importance of coronary venous pressure to the efficacy of coronary venous retroinfusion is demonstrated by the correlation between the derived myocardial concentration and the mean coronary venous pressure at the end of infusion.

Role of veno-venous shunting. Although coronary venous retroinfusion of metoprolol in most cases resulted in a high ischemic myocardial concentration, there was great individual variability. In fact, some pigs had lower concentrations in ischemic than in nonischemic myocardium (Table 4). The probable explanation is the effect of veno-venous shunts directing fractions of the retroinfusate directly into the cardiac chambers or the veins of the nonischemic area (26). The anatomy of veno-venous shunts shows great individual variability (27,28). In the presence of veno-venous shunting, coronary venous pressure would be expected to increase less than in situations where such shunts are scarce or absent. The pig in group A with the lowest ischemic myocardial drug concentrations also had the lowest mean coronary venous pressure and the pig in group B with the highest drug concentration also had the highest coronary venous pressure. There must, however, be other reasons for this great individual variability in myocardial concentration because significant variability was also seen after anterograde administration.

Study limitations. In this study, formal statistical comparisons of intravenous and coronary venous drug retroinfusion were made only on the basis of results with labeled and unlabeled metoprolol between pigs receiving retroinfused drug in "high" and "low" volumes and between anterograde and retrograde drug administration. The number of pigs used to study the importance of duration of coronary occlusion and the influence of flushing on myocardial concentrations was small. These groups were added only to illustrate two possible mechanisms of importance when discussing the pharmakokinetics of coronary venous retroinfusion of drugs. Nevertheless, the similarity between the results obtained in groups C and D and those in groups A, B and E suggests that the conclusions drawn from this study are justified.

Conclusions. Coronary venous retroinfusion results in pronounced and specific drug accumulation in ischemic myocardium with drug tissue concentrations similar to those obtained with anterograde coronary artery infusion. The high drug concentrations with retroinfusion do not appear to be the result of coronary venous trapping of drug. Drug distribution in ischemic tissue is similar to that achieved by anterograde administration. Retroinfusion does not cause any untoward accumulation of drug in nonischemic tissue; the retroinfused drug is evenly distributed in the ischemic area, but with a transmyocardial gradient.

In clinical practice, coronary venous retroinfusion may allow delivery of drugs into the ischemic myocardium when it is not possible to reach this area by anterograde administration. It may also permit delivery of very high myocardial concentrations of drugs, thereby improving the efficacy or changing the characteristics of cardioactive drugs. Another possible advantage may be the potential for administration of very expensive or rare drugs in small but still effective amounts by the coronary venous route, giving coronary venous retroperfusion an economical perspective.

We thank Myles Prevost and Willis Curtis Pea for valuable technical assistance in this study, Ronald Arzaga and Margit Andersson for careful preparation of the manuscript and Moraye Bear for excellent statistical advice.

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