CORONARY SINUS INTERVENTIONS: STATE OF THE ART AND INITIAL CLINICAL EXPERIENCE WITH RETROPERFUSION SUPPORT DURING ANGIOPLASTY

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In recent years there has been great interest in techniques to protect the ischemic myocardium via the coronary venous system. In the early 80s, some of these techniques were initially proposed to temporarily protect the ischemic myocardium in patients with rest angina refractory to medical therapy, as well as in patients with acute myocardial infarction. However, at that time, new emerging concepts about the importance of thrombosis in the pathogenesis of acute ischemic syndromes and the initial positive results of thrombolytic therapy in these patients drew most of the attention to the use of pharmacologic reperfusion in patients with acute myocardial infarction.

With the explosive development of coronary interventional therapy in the past few years, a renewed interest has emerged for the use of coronary sinus interventions to protect the jeopardized myocardium during such procedures. The ever increasing complexity of catheter-based intracoronary artery interventional procedures may require more prolonged interruption of blood supply distal to the interventional site, which in many instances imposes an unacceptable risk to the procedure, particularly in patients with high-risk anatomy of the coronary circulation. The coronary venous system is a unique route not only to supply the ischemic myocardium with nutrients but also with pharmacologic agents, mainly for three reasons: 1) ease of access; 2) absence of atherosclerosis and 3) the rich interconnections of the coronary venous system, which may facilitate delivery to practically all regions of the left and even right ventricle.

In this report we would like to review the basic principles of coronary sinus interventions and some of the potential applications of these techniques in man, with emphasis on coronary venous retroperfusion of autologous arterial blood.

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Supported in part by Grants HL 14644-15 and HL 17561-15 from the National Heart, Lung and Blood Institute, National Institute of Health, Bethesda, Maryland and the Medallion Group of Cedars-Sinai Medical Center, the Wallis Foundation, and Mrs Randolph Scott, Los Angeles, California.

Historical aspects of Coronary Sinus Interventions

In 1703, Thebesius reported his initial findings on the channels connecting the coronary vessels directly with the atria and ventricles[9], which were later named Thebesian veins. These observations provided the basis for subsequent studies on the anatomy of the coronary venous system, but it was not until the late 1800's that more detailed studies on the physiology of the coronary venous circulation were published. In 1893 Pratt[2] reported observations of coronary venous perfusion in excised hearts of dogs and cats and concluded that the coronary veins and Thebesian vessels were capable of providing sufficient blood flow to maintain continued and rhythmic myocardial contractions, including recovery from ventricular fibrillation. His findings were later confirmed by studies of Wearn[3], who demonstrated anastomoses between arterioles, venules and the left ventricular chamber in human hearts. He also found that these vessels were capable of draining up to 50% the coronary flow in the beating heart, and up to 90% in the nonbeating heart[3].

In 1938 Gregg and DeWald reported on a series of experiments in dogs in which the coronary venous system was partially occluded in order to encourage blood flow into infarcted areas of the heart[4,5]. Their conclusion from these early studies was that after acute ligation of the coronary sinus, coronary backflow in the left anterior descending artery was markedly elevated, but this highly unsaturated blood was not sufficient to prevent failure of contraction in the presence of left anterior descending coronary artery occlusion. Gross and Col[6] and Robertson[7] also demonstrated that partial or complete coronary sinus ligation resulted in increased myocardial blood supply and reduction in the size of infarcts and mortality. In the late 1940's, Beck and colleagues[8] pioneered the surgical retroperfusion procedure consisting of a shunt from the aorta to the coronary sinus, with subsequent ligation of the coronary sinus to increase the coronary venous pressure and perfuse the ischemic left ventricle. Initial positive results in experimental animals were followed by the socalled Beck II surgical retroperfusion procedure in approximately 200 patients[9]. The operation was abandoned a few years later due to high mortality rates and

complications associated with myocardial edema and hemorrhages secondary to excessive coronary venous pressures and impeded venous drainage.

In the early 1970's a renewed interest in coronary sinus interventions emerged, with new and again frustrating attempts of selective surgical arterialization of the coronary veins by anastomosis of the internal mammary artery to the coronary veins[10-12]. Catheterbased coronary venous retroperfusion was introduced by Meerbaum and Corday in 1976[13] and this has stimulated great interest in coronary sinus interventional research in the past decade.

Modalities of Coronary Sinus Interventions

Synchronized Diastolic Retroperfusion (SRP): This technique, originally conceptualized and developed in our laboratory, employs a specially designed balloon-tipped coronary sinus catheter. Arterial blood is shunted from the femoral artery using an 8 French withdrawal catheter with an end and sideholes which is connected to the inlet tubing of a

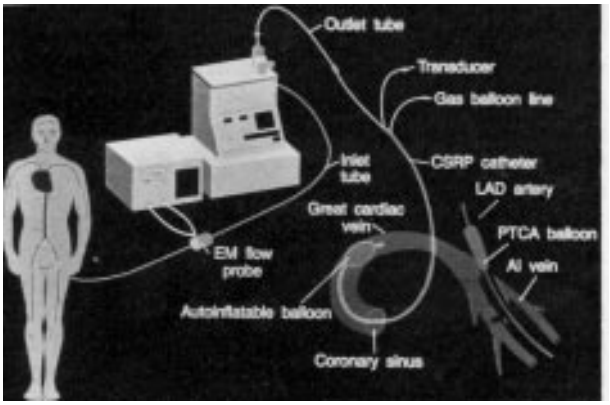

Fig. 1 — Schematic of the coronary sinus retroperfusion (CSRP) technique. See text for details (PTCA = percutaneous transluminal coronary angioplasty; LAD = left anterior descending: AI = anterior interventricular; EM = electromagnetic).

disposable pumping cassette. The cassette is aligned within the electronic housing of the console and arterial blood is pumped in diastole by means of a piston activated by ECG triggering. The outlet of the pumping cassette is connected to the SRP catheter (fig. 1).

At least three elements were critical in the development of this system. First, the synchronized inflation of the balloon in diastole, which occludes the coronary sinus (or great cardiac vein) and causes the infusate to be delivered retrogradely into the ischemic myocardium; in systole, flow is stopped and rapid balloon deflation allows normal coronary venous drainage. The second important element was the development of the triple-lumen balloon-tipped catheter, currently used in clinical trials. The infusion lumen is connected to the outlet tubing of the pumping cassette, the second lumen is used to inflate the balloon (10 mm balloon diameter, oval-shaped at full inflation pressure) with a fixed volume of CO_2 through a pressurized cylinder in synchronization with each pump stroke during diastole, and the third lumen serves to continuously monitor coronary venous pressures prior to and during SRP (fig. 2). The third important aspect in the design and development of the pump was the issue of safety, particularly damage to blood elements and coronary veins. The capability of

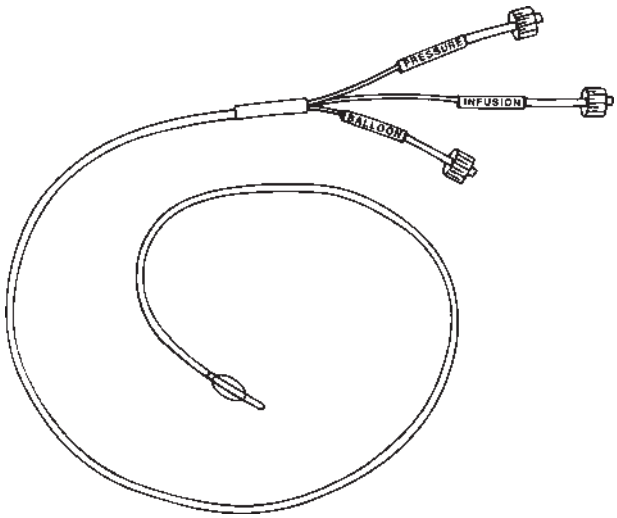

Fig. 2—Schematic of the triple-lumen balloon-tipped retroperfusion catheter. See text for details.

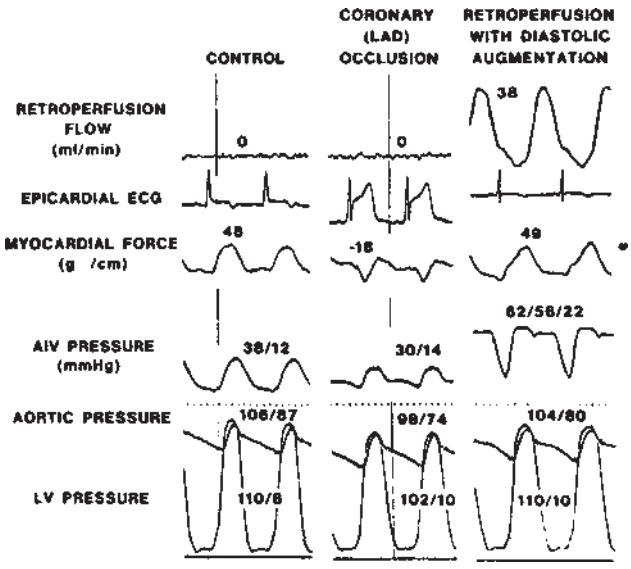

Fig. 3—Changes in anterior interventricular vein (AIV) pressure, epicardial ECO, myocardial contraction (myocardial force) and hemodynamics during diastolic retroperfusion (38 ml/min) in a dog following left anterior descending (LAD) coronary artery occlusion. Retroperfusion caused return of myocardial contraction, systolic pressure and epicardial ST segment elevation to preocclusion conditions. The AIV diastolic pressure was increased during retroperfusion pumping to 56 mmHg (from Meerbaum et al, reference 13, with permission from the author and the American Journal of Cardiology).

pumping arterial blood up to 250 ml per minute has been recently developed and represents an important additional feature of the system.

Several steps had to be overcome before SRP could be applied in the human. This took several years of research and development in the animal laboratory, initially using prototype catheters and pump systems, until more appropriate and acceptable devices were developed that could be used in patients. Optimization of coronary venous pressures and flows was essential not only for improving the efficacy but also the safety of the technique. Our initial studies in the dog taught us that excessive pressures in the coronary venous system were usually associated with damage to the coronary veins and myocardial hemorrhages. We found that peak coronary venous pressures up to 60-65 mmHg (or mean pressures up to 40 mmHg) were not associated with such complications[13-14]. Figure 3 shows typical changes in coronary venous pressures during SRP in a dog experiment during left anterior descending (LAD) coronary artery occlusion. As demonstrated, coronary venous pressure increases during SRP, particularly during diastole, and pressure decreases when SRP is discontinued during systole.

The mechanism of retroperfusion. The rationale for retroperfusion relies mainly on the beneficial effects of retrograde delivery of arterial blood to the ischemic area. The amount of retroperfused blood seems to be directly related to the pressure gradients between the coronary veins and the left (or right) ventricular cavity, particularly in diastole, as well as the pressure differences between the regional veins and the coronary artery distal to the site of obstruction. It is noteworthy that retroperfusion is not effective when epicardial coronary artery blood flows are normal, nor does it seem to perfuse myocardium when coronary venous pressures are very low[15-18]. Taira and colleagues have recently demonstrated that during retroperfusion in the presence of ischemia, the increase in coronary venous pressure is flow dependent[16]. In their study a practically linear correlation was found between coronary venous flow during retroperfusion and coronary venous pressure.

Under ischemic conditions, it is likely that vasodilatation in the ischemic area, highly compliant epicardial vessels, as well as reduced myocardial contraction may facilitate retrograde perfusion. It is not known, however, to what extent intramyocardial stresses and extravascular resistance to flow would reduce the magnitude of retroperfused blood. Snyder and col[19] have studied the components of extravascular resistance to coronary artery flow and concluded that intraventricular pressure is the major determinant of extravascular resistance, whereas contractility has only a slight effect on extravascular compression of resistance vessels.

Another possible determinant of diastolic retrograde flow during retroperfusion is the diastolic pressure gradient within the left ventricular (LV) wall itself. Stein and col[20] measured diastolic intramyocardial pressures in open-chest dogs and found signifincat gradients between the subepicardial and subendocardial layers, and LV end-diastolic pressures. In their study, subepicardial pressures measured with high-fidelity micrometers averaged 28 mmHg, whereas subendocardial and LV end-diastolic pressures measured 13 and 8 mmHg, respectively. These diastolic pressure gradients have been previously predicted from pressure-flow curves of the coronary circulations[21,22], and the direction of this gradient is reversed compared to the gradients observed during systole. Armour and Klassen measured central and peripheral epicardial coronary venous pressures in the canine and found that central coronary venous pressures (near the coronary sinus) were much lower than peripheral venous pressures measured at the apex of the heart, and that peripheral coronary artery and venous pressures had similar wave forms[23]. They concluded that intramyocardial pressures have an important effect upon coronary venous pressures.

Myocardial compression due to venous engorgement and increased intramural blood volume is unlikely to occur during high-flow retroperfusion, because excessive coronary venous blood would probably drain through the Thebesian veins into the heart chambers, unless ventricular end-diastolic pressures are exceedingly high. Under these conditions, it is possible that concurrent unloading of the ventricle may be necessary to enhance delivery of blood during SRP.

Increased diastolic coronary venous pressure during SRP may also enhance flow across Thebesian venous-capillary connections, but to what extent this increased flow will translate into myocardial nutrition will largely depend upon the ability of this arterialized blood to give up oxygen during the passage through the capillaries. Meerbaum and col[13] previously noted a consistent reduction in arterial pO_2 distal to the site of LAD occlusion during SRP, which could serve as an indirect evidence of oxygen utilization by the ischemic myocardium. However, the authors did not exclude other possible explanations for this observation, such as retrograde displacement of the coronary venous effluent into the ischemic distal arterial bed.

It is important to recognize that Thebesian flow, which seems to be highly variable among and within mammalian species, may in fact be a double sword in the ability of retroperfusion to provide nutrient flow to the ischemic myocardium. On one hand, Thebesian vessels may serve as an escape

valve to exceedingly high venous pressures during retroperfusion; on the other hand, excessive Thebesian flow may preclude the retroperfusate to reach the ischemic myocardium. Maurer and col[24], using contrast echocardiography, have recently demonstrated opacification of the ischemic myocardium with coronary venous injections of echocontrast agents in the canine, however they also noted significant shuntings to all heart chambers but the left atrium, and stated that these shunts could diminish the efficacy of retroperfusion interventions because only a fraction of the retroperfusate would reach the ischemic myocardium. A previous study by Scharff and col[25] in the isolated perfused dog heart preparation[25] has demonstrated that more than 80% of the coronary venous flow drained directly into the right heart chambers when coronary sinus pressure exceeded 35-40 mmHg. More recently, Ten Cate and col[26] and Zwehl and col[27] in preliminary studies in humans using newer echo-contrast agents, have also demonstrated Thebesian flow to the LV cavity, both in the beating heart[26] and in the arrested heart during cardiac surgery[27]. Another indirect evidence of extensive Thebesian flow in humans was provided in a study by Faxon and col[28]. These authors found that LV end diastolic pressure was very similar to coronary sinus occlusion pressure in diastole, and suggested that the latter could be used to assess LV filling pressure in man, although they did not exclude the possible contribution of transmitted intramyocardial pressure[20].

The effects of SRP on hemodynamics have been extensively investigated in experimental animals[13,14], but these effects are still ill-defined in the human. Thus, it has been shown that SRP reduces systemic vascular resistance in the canine[14], while increasing cardiac output in the presence of acute LAD coronary artery occlusion. Systolic blood pressure and LV enddiastolic pressure as well as heart rates seemed to be slightly reduced in this model[14].

Gore and col[29] reported no changes in right heart pressures, systolic blood pressure, cardiac output and heart rate in a limited number of patients with rest angina treated by SRP for a mean of 28 hours. In recent preliminary reports of SRP support during percutaneous transluminal coronary angioplasty (PTCA), SRP increased cardiac output and LV stroke work in one study[30], but failed to improve diastolic function in another study[31].

A second possible mechanism of SRP may be related to washout of metabolites from the ischemic myocardium, as proposed by Farcot and col[14] and recently demonstrated by Chang and col[32]. It is known that in the presence of very low flows in the ischemic zone metabolites tend to rapidly accumulate, leading to accelerated ischemic injury and myocardial dysfunction[33,34]. Enhanced washout of metabolites during myocardial ischemia has also been demonstrated with the use of pressure-controlled intermittent coronary sinus occlusion and measurements of coronary arteriovenous differences of blood density gradients in the microcirculation[35,36]. Our laboratory[13,14,37] and others[38,39] have found 40 to 50% reduction in infarct size after 4 to 6 hours of LAD coronary artery occlusion in the dog[14,37], as well as in the baboon[38,39]. Improvement in ischemic zone LV systolic function in the canine was found early[40], and late[13,14] during SRP in the presence of LAD occlusion, although function did not return to preocclusion levels.

In spite of extensive animal research, there were arguments citing the lack of direct evidence of increased nutrient myocardial blood flow during SRP, mostly because of the fact that the radioactive microsphere technique, which is the most acceptable method of measuring regional myocardial blood flow in experimental animals, has not been successfully used in the setting of SRP. This may be due to the fact that the SRP flow itself precludes trapping of microspheres in the myocardial regions being retroperfused. More recently, experimental studies using positron emission tomography have clearly demonstrated not only increased myocardial nutrient flow during SRP but also preservation of metabolic activity, using flow and metabolic tracers in the same experiments[41].

Hypothermic synchronized retroperfusion (HSRP). Another interesting modality of SRP is the cooling of arterial blood while it is being retroperfused. This is accomplished by a simple interposition of a cooling coil between the outlet tubing of the pump and the retroperfusion catheter. The combination of increased blood supply by SRP with reduced myocardial oxygen demands associated with myocardial coolings has been shown to further improve regional ischemic LV function and reduce infarct size[42]. HSRP during LAD occlusion followed by anterograde reperfusion was also associated with reduced infarct size and less reperfusion injury and arrhythmias[43]. In our laboratory, we have used blood infusate temperatures in the order of 10 to 20ºC, which will induce a reduction of myocardial temperatures of 5 to 8ºC in the openchest canine preparation. In closed-chest dogs, HSRP has been found to reduce infarct size by 60 to 80%[42-44], while improving regional wall motion abnormalities (fig. 4 and 5).

Pressure-Controlled Intermittent Coronary Sinus Occlusion (PICSO). This thecnique was first described by Mohl and col in 1984[45]. Unlike SRP, the mechanism of PICSO during myocardial ischemia is not arterialization but rather manipulation of the coronary venous pressure and blood drainage[35,36]. The mechanism and effectiveness of PICSO appears to be based

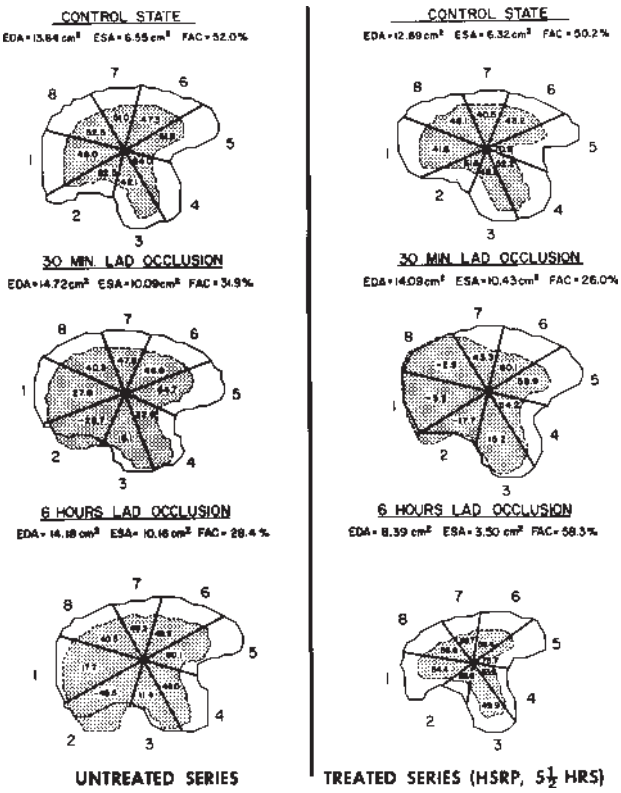

Fig. 4—Evaluation of the effectiveness of hypothermic synchronized retroperfusion (HSRP) on left ventricular (LV) contraction abnormalities induced by controls (left panel), 5.5 hours of HSRP improved segmental wall motion and reduced LV volumes. The continuous outlines represent end-diastolic endocardial contours of mid LV two-dimensional echographic short-axis views, and the dashed lines represent the end-systolic contours. The numbers in each of the octants represent the fractional area change (FAC) for that region. EDA = sectional end-diastolic area; ESA = end systolic area (from Haendchen et al, reference 44, with permission from the publishers).

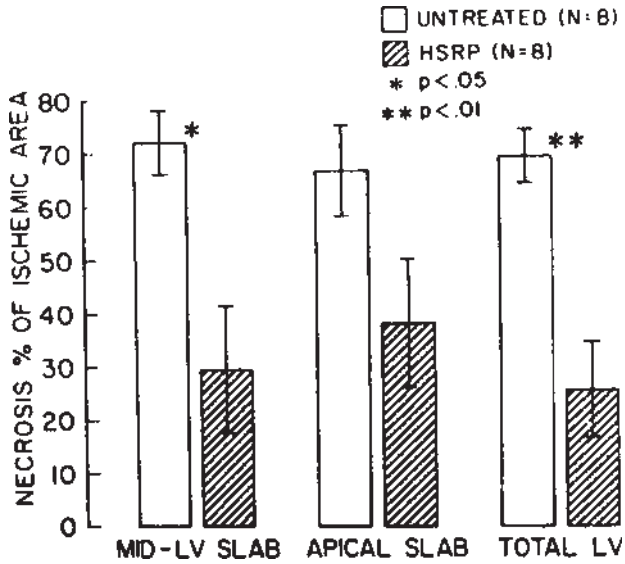

Fig. 5—Myocardial necrosis expressed as percent of ischemic area, in dogs with 6 hours of untreated left anterior descending coronary artery occlusion compared to hypothermic synchronized retroperfusion (HSRP) treatment from 30 minutes to 6 hr LAD occlusion. Necrosis was measured with the triphenyl-tetrazolium-chloride technique in apical and mid left ventricular (LV) 1 cm thick slabs perpendicular to the LV long axis, and ischemia measured by glycogen depletion in alternate slabs (from Meerbaum et al, reference 42, with permission from the author and the American Heart Association).

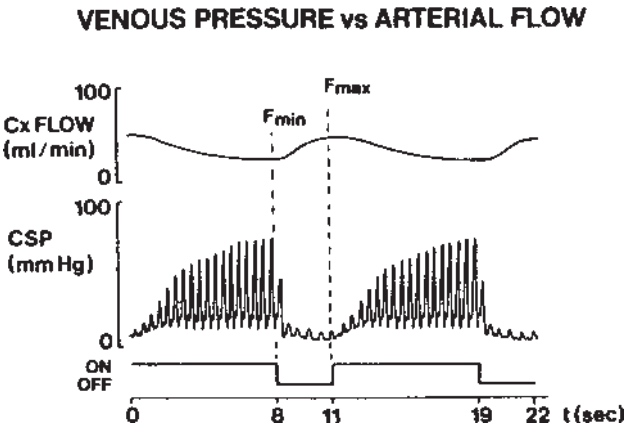

Fig. 6—Coronary sinus pressure (CSP) during pressure-controlled intermittent coronary sinus occlusion (PICSO) and its effects on mean circumflex coronary artery blood flow (Cx Flow) measured with electromagnetic flowmeter. The maximum Cx Flow (F max) is used for the development of an algorithm for CSP control (ON/OFF phases) to determine closed-loop control during PICSO. Note that minimum Cx Flow (F min) occurs when the systolic pressure plateau is reached during PICSO (i.e., 95% of the predicted plateau value). See text for details (from Mohl W, reference 97, with permission from the author and the American Heart Association).

upon washout of toxic metabolites from the ischemic zone (so called washout phase) and retrograde perfusion of residual substrate content of venous blood (redistribution phase). Figure 6 shows typical coronary sinus pressures during PICSO and concomitant left circumflex coronary artery blood flow measured with electromagnetic flowmeter. Appropriate timing of coronary sinus occlusion and release phases during PICSO is, according to these investigators, crucial for the salutary mechanism of PICSO[36]. In other words, the coronary sinus occlusion phase should not be too short and cannot be too long. Experimental studies in dogs indicated that PICSO improves regional ischemic function during coronary artery occlusion[46] and reduces infarct size[47], whereas a recently published study reported that intermittent coronary sinus occlusion without adjustment of the occlusion release phases did not reduce infarct size[48].

Coronary Venous Retroinfusion Techniques. Two conditions which have been investigated with coronary venous retroinfusion of pharmacologic agents or solutions are: a) retrograde cardioplegia during cardiac surgery, and b) drug retroinfusions in the beating heart.

Retrograde cardioplegia. There have a number of experimental and also clinical studies comparing the efficacy of retrograde versus antegrade cardioplegia[49-51]. Lillehei and col[52] reported on the use of hypothermic retrograde perfusion of the coronary sinus during aortic valve

surgery as early as 1956[52,53]. Retrograde cardioplegia can be delivered directly through coronary sinus infusions or indirectly into the right atrium. It has been shown that retrograde coronary sinus cardioplegia provides more slow and uniform distribution of cardioplegic solutions and cooling, particularly in patients with extensive multivessel coronary artery disease[51].

There has been considerable debate in recent years as to whether retrograde coronary sinus cardioplegia might be superior to antegrade cardioplegia for myocardial protection during open-heart surgery. In 1982, Menashe and col[54] reported on a large number of patients undergoing aortic valve surgery with antegrade or retrograde potassium hypothermic cardioplegia.

Their results indicated that the retrograde method was associated with better postoperative LV function and less myocardial damage. In a randomized study in patients undergoing coronary artery bypass surgery, Guiraudon and col[55] found no differences in preservation of myocardial function or serum enzymes among subjects submitted to retrograde as opposed to antegrade cardioplegia. Shapira and col also reported more uniform myocardial cooling with retrograde compared to antegrade cardioplegia during coronary surgery[56].

There has also been some concern about inadequate right ventricular protection with retrograde cardioplegia[57-59], in patients with severe right coronary artery obstructive lesions, leading to postoperative right ventricular dysfunction and failure. However, a recent study by Eichhorn and col[60] in patients with severe right coronary artery lesions undergoing coronary artery bypass surgery indicated that right atrial cardioplegia protects the right ventricular myocardium during surgery. These authors found no differences in postoperative systolic or diastolic right ventricular function among 20 patients randomized to right atrial or antegrade cold blood cardioplegia. Menasche and col[61] reported similar results on right ventricular function using coronary sinus cardioplegia, provided that the perfusion catheter did not obstruct the terminal tributaries of the coronary sinus, allowing delivery of the cardioplegia solution to right-sided cardiac structures. Shaper and cold[62] studied LV biopsies in 42 patients during cardiac surgery and compared the ultrastructural changes in the myocardium protected by antegrade versus retrograde crystalloid cardioplegia. They concluded that retrograde continuous perfusion of cardioplegic solution offers better protection of myocytes from ischemic injury. However, these authors also found more extracellular edema and microvascular damage with the retrograde method, in spite of maintaining a perfusion pressure of 30 mmHg. There were no differences in ischemic time or number of bypasses between the two groups in that study.

There seems to be a consensus among cardiac surgeons that in patients with severe and extensive coronary artery disease, homogeneous distribution of cardioplegic solutions and cooling of the heart are usually not achieved by anterograde cardioplegia, resulting in inadequate myocardial protection of some regions of the heart[51]. In such patients, retrograde cardioplegia appears to be superior to the antegrade conventional methods. Patients with extensive aortic valve disease requiring not only valve replacement, but also coronary bypass surgery, are also good candidates for retrograde cardioplegia. In cases of aortic insufficiency, the retrograde methods prevent the inadequate distribution of cardioplegia solutions associated with anterograde cardioplegia, as well as potential complications related to coronary artery ostial cannulation, namely coronary artery dissection and late ostial stenosis secondary to vessel injury and local smooth muscle cell proliferation. In patients with aortic valve stenosis the antegrade perfusion methods have two potential disadvantages compared to retrograde cardioplegia, that is, coronary artery ostial cannulation and interference with the surgical field. In several centers, either coronary sinus or right atrial cardioplegia have been frequently used in such cases[51,60,61]. Definitive answers regarding superiority of retrograde versus antegrade cardioplegia in several subgroups of patients will probably require larger randomized studies.

Retroinfusion on Pharmacologic Agents in the Beating Heart. A number of experimental studies have reported superior results of coronary venous infusion compared to systemic intravenous infusion of infarct reducing agentes, particularly in the setting of acute LAD coronary artery occlusion[63-67]. The rationale for the use of retrograde coronary venous drug delivery in this setting is that with systemic administration the myocardial drug concentration beyond the occluded coronary artery would be nonpharmacologic and therefore preclude the potential local beneficial effect of the agent. Indeed, in recent studies in our laboratory using[68] simultaneous infusions of tritium labeled metoprolol in the great cardiac vein and unlabeled metoprolol in the right atrium, after 30 minutes of LAD ligation in pigs, Ryden and col found that 1) there was veryn little metoprolol in the ischemic myocardium following right atrial infusions: 2) ischemic zone myocardial drug concentrations were 10 to 500 times higher following great cardiac vein compared to right atrial infusions; 3) there was a gradient of metoprolol concentration between subendocardial, midmyocardial and subepicardial regions after retrograde infusions, with tissue metoprolol levels being significantly higher at the midmyocardial and subepicardial layers; 4) plasma

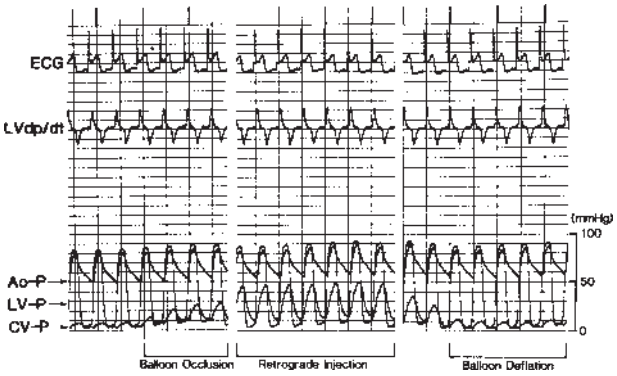

Fig. 7—Coronary venous pressure (CV-P) measurements during CV drug infusions. Note that CV-P gradually increases during oclusion of the coronary sinus (balloon occlusion). Drug infusion is performed when CV-P reaches a plateau (retrograde injection) followed by rapid reduction of CV-P after balloon deflation. AoP = aortic pressure, LV-P = left ventricular pressure, LV dP/dt = maximum rate of rise and decline of LV-P.

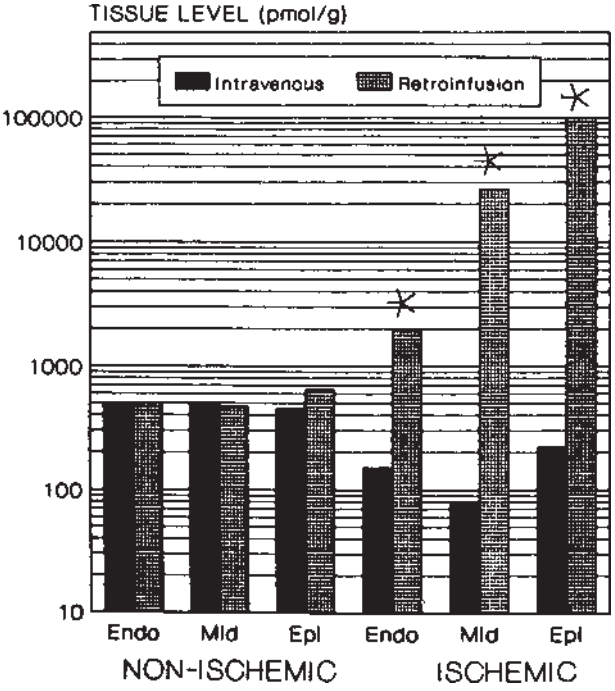

Fig. 8—Metoprolol concentration in myocardial tissue (measured by gas chromatography mass spectrometry) in ischemic and nonischemie regions following systemic intravenous or coronary venous retroinfusion. In the nonischemic regions, tissue concentrations averaged 450-500 pmol/g in subendocardial (endo), midmyocardial (mid) and subepicardial (epi) regions. In ischemic regions, metoprolol concentrations were lower than in nonischemic regions after intravenous administration; after coronary venous metoprolol retroinfusion, myocardial drug concentrations were significantly higher compared to intravenous infusions, particularly in the mid and subepicardial regions. Please note that the Y axis is in logarithmic scale. (* p< .05 vs intravenous at endo regions, and p < .01 at mid and epi regions). Adapted from Ryden et al, reference 69, with permission from the author and the Journal of Cardiovascular Pharmacology.

levels of metoprolol were significantly higher only very early (5 min) after intravenous infusions compared to the same amount given in the great cardiac vein[69]. In another study[70], Ryden and col compared myocardial concentrations of metoprolol given retrogradely or in the coronary artery distal to the occlusion site and found no significant differences in myocardial drug concentrations in the ischemic zones.

The method of coronary venous drug retroinfusion used in our laboratory has been described in detail elsewhere[64,66,69]. Briefly, immediately before drug retroinfusion, the balloon at the tip of the retroinfusion catheter is inflated and the drug retroinfused through the infusion lumen of the catheter. The balloon is kept inflated for approximately 2 minutes to prevent the drug from regurgitating back into the right atrium (fig. 7). The distribution of the beta adrenegic blocker metoprolol in ischemic and nonischemic myocardium using this technique was measured with gas chromatography mass spectrometry[69]. These results are illustrated in figure 8. Therefore, there is no question that high myocardial drug concentrations can be achieved in the ischemic zone

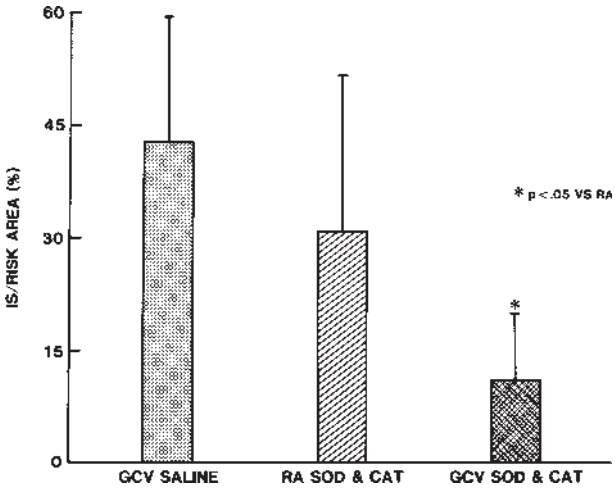

Fig. 9—Infarct size (IS) expressed as percent of risk area in dogs treated with great cardiac vein (GCV) retroinfusion of the oxygen free radical scavenger superoxide dismutase and catalase (SOD & CAT) given 15 minutes prior to reperfusion following 90 minutes of left anterior descending coronary artery occlusion. Compared to right atrial (RA) administration of SOD & CAT or to placebo (GCV saline), infarct size was much smaller following GCV retroinfusion. (Adapted from reference 75, with permission from the author and the Journal of Cardiovascular Pharmacology).

by retrograde coronary venous infusions, compared to systemic intravenous administration.

These findings may have some important clinical implications, particularly in the setting of acute coronary artery occlusion, since several cardioprotective agents ideally should achieve their pharmacologic effects at the site of injury. A typical example would be the use of oxygen free radical scavengers immediately prior to reperfusion. We believe that adjunctive therapy to reperfusion is of clinical significance, but there is a need to test more effective drug delivery methods prior to and during the initial phase of reperfusion. In this case the

intravenous administration of a drug which has a potential local beneficial effect on ischemic myocardium may not even be relevant in the presence of coronary artery occlusion and limited collateral blood flow, since therapeutic concentrations may not be achieved at the site where the drug is mostly needed. Indeed, a recent clinical reperfusion study[71] employing iloprost, a stable analogue of prostacyclin, previously shown to reduce infarct size in animal models[72-74] failed to demonstrate beneficial effects when given intravenously in patients with acute myocardial infarction undergoing thrombolytic therapy. Our experimental studies, comparing the use of right atrial versus great cardiac vein infusions of the oxygen free radical scavenger superoxide dismutase and catalase prior to reperfusion in dogs with LAD occlusion[75], have shown significantly better results in terms of infarct size reductin and reginal systolic function using the retrograde drug infusion protocol (fig. 9). These differences were even more pronounced in the pig model, possibly because of much lower collateral flow in the swine compared to; the canine[77].

Other potential applications of coronary venous drug retroinfusion include retrograde thrombolysis with more prolonged, continuous local delivery of smaller dosages of thrombolytic agents. We have previously demonstrated in the experimental laboratory that retroinfusion of streptokinase[64] or tissue plasminogen activator[78] was associated with much faster lysis of thrombotic LAD coronary artery occlusions compared to the same amount of drug given systemically. Retroinfusion of streptokinase[64] or tissue plasminogen acof coronary angioplasty is another area of potential clinical application, as is the use of antiarrhythmic agents in cases of refractory, sustained, life—threatening arrhythmias. Experimental studies in dogs have indicated that retrograde infusion of procainamide was more effective to terminate sustained induced ventricular tachycardia compared to intravenous administration[66]. In that study, myocardial procainamide concentrations were approximately 15 times higher with great cardiac vein versus systemic intravenous infusions.

Coronary venous retroperfusion in man

Intracoronary interventional therapy for obstructive coronary artery disease is one of the most rapidly developing fields in cardiology today. However, as the complexity of intra-arterial interventional procedures increases, and more and more high-risk patients are being treated[79], there is an unquestinable need for developing techniques to supply the ischemic myocardium with arterial blood during such interventions, particularly in patients with high-risk coronary anatomy and/or poor LV function. Hemodynamic support is also frequently needed when these procedures are complicated by abrupt coronary artery closure, hypotension and shock, or refractory ventricular fibrillation[80].

Several devices are now being tested in preliminary clincal trials, some of them aimed at providing exclusively hemodynamic support[8186] whereas other methods[87-90]including SRP primarily provide myocardial blood supply, hoping that the hemodynamic status of crashed patients will improve if enough blood reaches the acutely ischemic, noncontracting regions of the myocardium. Some of these techniques can even maintain an adequate blood pressure and peripheral perfusion in patients during ventricular fibrillation or asystol, such as the percutaneous cardiopulmonary bypass devices, although is does not provide direct myocardial blood supply. However, systemic circulatory support and techniques designed to supply blood flow to ischemic myocardium are not mutually exclusive, and there are clinical situations in which the combination of the two will be the best approach to support high-risk procedures or to rescue patients when severe complications occur.

The use of SRP in the catheterization laboratory requires understanding of a few practical aspects of this technique. First, the venous access used for catheterization of the coronary sinus has varied among investigators. In our own institution, the internal jugular vein has proved to be a rapid route for catheter insertion, although anomalous venous anatomy in the neck may occur, and other alternatives should always be available. Some investigators have used a cutdown and the left (or right) brachial approach, while others have preferred percutaneous insertion through the left subclavian vein or the femoral venous route. In a relatively small percentage of patients, the entrance of the coronary sinus is small (particularly in women of small body weight), which may present difficulties for catheter insertion. In patients with previous cardiac surgery it may also be more difficult to catheterize the coronary sinus.

Another important point is the location of the tip of the STR catheter. For SRP of the LV anterior wall, we find that with the currently used catheter, its tip should be positioned in the great cardiac vein, in the vicinity of the anterior interventricular vein but without wedging the catheter. For retroperfusion of the areas supplied by the left circumflex or even right coronary artery, including the right ventricular free wall, there is not enough data to support the theoretically sound idea of positioning the SRP catheter proximally in the coronary sinus. Nevertheless, recent clinical data using retrograde cardioplegia in the arrested heart indicates that positioning of the retroperfusion catheter proximal to the entrance of the posterior

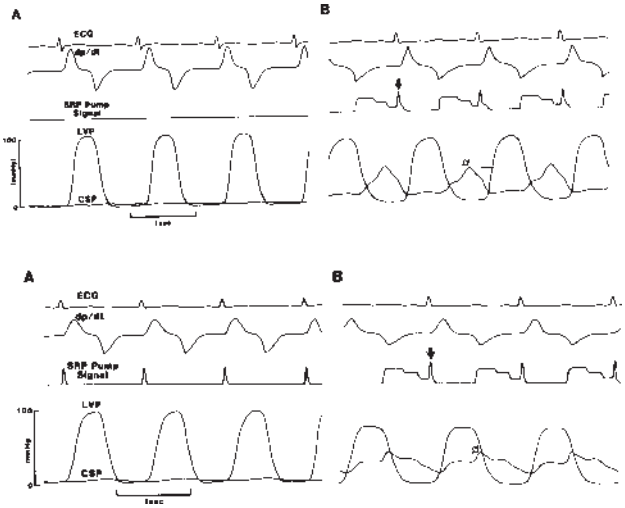

Fig. 10—Coronary venous pressures during synchronized retroperfusion (SRP).
Top panel A) Baseline ECG, left ventricular pressure (LVP), rate of rise and decline of the LVP (dP/dt) and coronary sinus pressure (CSP); B) Note appropriate triggering (black arrow) of the pump signal concomitant with the R wave on the ECG during SRP, and adequate timing of CSP rise and peak CSP (open arrow) in this case.
Bottom panel A) Before SRP; B) during SRP. In this experiment, in spite of appropriate R wave triggering of the SRP pump signal, CSP begins to rise during systole and peak CSP occurs too early (open arrow). Inappropriate phasing of CSP may occur with the use of intrinsically built pressure delay systems, particularly in the setting of bradyeardia (as in this case) and/or prolonged QT intervals.

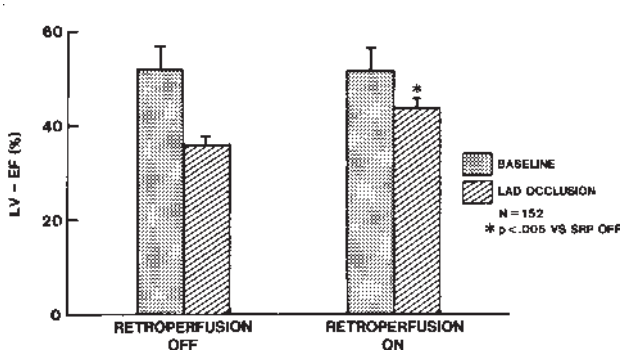

Fig. 11—Global left ventricular ejection fraction (LV-EF) in patients undergoing retroperfusion-supported percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending (LAD) coronary artery. PTCA-induced LAD occlusions were alternatively untreated or treated by synchronized retroperfusion (SRP). LV-EF dropped from a baseline of 52% to 35% in untreated PTCA balloon inflations, whereas it was reduced to only 44% during retroperfusion-supported LAD occlusions. See text for details.

interventricular vein and other terminal tributaries of the coronary sinus was crucial for protection of the right ventricle during aortic valve surgery[61].

Once the SRP catheter is appropriately positioned, coronary venous pressures should be recorded to assure that the catheter is not wedged. This should be followed by contrast venography to detect any possible large venous shunts, in which case SRP should not be pursued. While monitoring coronary venous pressures, SRP flow rates should be gradually increased to the maximum output of the currently used system (250 ml/min), or until peak coronary venous pressure in diastole reaches 60-65 mmHg (or mean pressure of 45-40 mmHg). Timing of coronary venous pressure rise and peak pressure should be appropriately adjusted to occur during the diastolic phase, avoiding excessive pressures during ventricular systole. Figure 10 shows an example of inappropriate timing of coronary venous pressure rise during SRP.

Retroperfusion support during PTCA

Coronary venous retroperfusion support was used in 152 patients with stable angina undergoing PTCA of the LAD coronary artery. These patients were part of a multicenter trial and many of them were included in the study because they were considered relatively high-risk candidates for PTCA[92]. Short duration PTCA balloon occlusions of the LAD coronary artery were alternatively untreated or treated by SRP, and all these patients had a minimum of two PTCA balloon inflations. Hemodynamics, severity and onset of chest pain during LAD occlusion, ST segment shifts, and regional wall motion as well as global LV ejection fraction by two-dimensional echocardiography were monitored during the procedure. Coronary venous pressures were also monitored throughout the studies, and SRP flow rates ranged from 50 to 250 ml/minute.

Angina occurred in 60% of the untreated PTCA balloon inflations at 38 ± 15 sees. These differences were statistically significant. The magnitude of ST segment change was also significantly reduced duringSRP treated PTCA balloon inflations compared to untreated occlusions. Global LV ejection fraction was reduced from a baseline of 52% in both groups to 36% in untreated, as opposed to 44% in SRP treated LAD coronary occlusions during PTCA (fig. 11). These beneficial effects of SRP were mostly due to maintenance of regional wall motion in the area rendered ischemic during PTCA. There were no significant changes in heart rate or systolic blood pressure between the groups. Out of the 152 patients undergoing SRP supported PTCA, 5 patients developed abrupt coronary artery closure following PTCA. These patients were maintained on SRP for approximately 4 ± 2 hours before undergoing emergent coronary artery bypass surgery. Despite prolonged pre-operative myocardial ischemia and prolonged SRP pumping, all patients did well post-operatively, and there was no damage to the coronary sinus, regional veins or myocardium noted by the surgeons at the time of surgery.

It is important to note that in the first 23 cases performed in our institution, the coronary sinus was successfully catheterized in 20 (87%) patients. In two patients the coronary sinus could not be catheterized and in another patient there was difficulty in entering the internal jugular vein. More

recently, successful coronary sinus catheterization was possible in 93% of the cases, and within less than 5 minutes in the majority of patients. There have been no serious complications or deaths related to the procedure itself. Hematomas at the site of the insertion of the catheter in the neck occurred in less than 10% of the cases without the need for blood transfusion.

Transient atrial arrhythmias or atrial fibrillation at the time of placement of the SRP catheter has occurred in a small percentage of cases. Peak coronary venous pressures during SRP in the majority of patients have been much lower (20 to 30 mmHg) than those found in the canine.

These initial trials have demonstrated the safety of SRP in humans. Although SRP was clearly effective in the majority of cases, this protocol was not specifically designed to test efficacy of this technique. Studies are currently underway to assess SRP efficacy in several clinical situations.

Retroperfusion in patients with unstable angina

In 1986, Gore and col[29] reported on the use of SRP in five patients with unstable angina refractory to maximal medical therapy. All patients had significant ischemia of the anterior wall documented by more than 1.5 mm of ST segment elevation or depression in two consecutive ECG leads in spite of optimal medical therapy, including intravenous nitroglycerin. Using a mean SRP flow of 103 ml/minute continuously for a mean of 28 hours, these authors concluded that SRP was safe, it did not significantly change heartrate, arterial blood pressure, right heart pressures or cardiac output, and more importantly, they noted relief of symptoms within 10 minutes of SRP, and recurrence of angina when SRP was discontinued in 4 out of 5 patients. The long period of observation in their study, along with electrocardiographic and clinical evidence of reduction in myocardial ischemia, indicate clinical benefit in these patients.

In another preliminary report, Costantini and col[30] used SRP support in patients with rest angina undergoing PTCA. This was a high-risk group of patients with low LV ejection fractions or large areas of myocardium at risk. The authors concluded that during SRP treated PTCA balloon inflations, LV ejection fraction, stroke work and cardiac output were significantly better compared to untreated inflations the same patients.

Potential Adverse Effects of Coronary Sinus Interventions

Percutaneous catheterization of the coronary sinus should be performed by experienced operators and under fluoroscopic guidance. Even under ideal circumstances, there is a small but not negligible risk of acute complications related to the catheterization procedure itself, such as perforation of the right atrium or the coronary sinus. Transient atrial arrhythmias may also occur in a small percentage of cases, including atrial fibrillation.

The safety of prolonged SRP has been previously studied in both experimental animals[13,14,34,93] and in humans[29]. These studies have demonstrated no evidence of significant red cell hemolysis or platelet destruction, no significant damage to the coronary venous system, and no significant myocardial edema or hemorrhages during SRP in dogs with LAD coronary artery occlusion, provided that peak coronary venous pressure during SRP did not exceed 60 mmHg[13,14,37,] Gore and col[93] reported the effects of upo to 24 hour continuous SRP in dogs at flow rates of 50 ml/minute. They found no significant macroscopic changes in the coronary veins but on microscopic examination the superficial layer of endothelial cells in the coronary sinus was replaced by a thin layer of fibrin. This was probably related to rubbing of the catheter in the coronary sinus and may have also been due to repetitive inflations of the balloon at the tip of the SRP catheter. Small, nonocclusive thrombi were also found in some instances, particularly if anticoagulation was not appropriate.

In a number of patients who developed abrupt coronary artery closure following PTCA and underwent subsequent emergent coronary artery bypass surgery in our institution[92], there were no significant macroscopic changes in the coronary veins or myocardium noted during surgery. Nevertheless, the longterm effects of endothelial cell damage and repetitive overdistention of the regional coronary vein during SRP in human beings have not been studied (the diameter of the inflated balloon at the tip of the SRP catheter exceeds the diameter of the regional coronary vein). It is possible that this vessel injury may induce local smooth muscle cell proliferation in the venous wall and late stenotic lesion of the regional vein. The same applies to the use of PICSO.

During retrograde cardioplegia in the arrested heart, care must be taken to avoid direct damage during catheterization, and mean perfusion pressures should not exceed 35 to 40 mmHg. Swelling of the coronary sinus vascular endothelium and extracellular edema have been reported in patients undergoing coronary artery bypass surgery with delivered coronary sinus cardioplegia[62].

Limitations of Coronary Sinus Interventions and Future Directions in Research

There are several unanswered questions that need to be addressed in the near future, particularly with respect to improved efficacy of SRP in patients

with acute LV anterior wall ischemia, and also the potential of SRP to protect ischemic myocardial regions supplied by the left circumflex or right coronary arteries. Also, the potential use of PICSO to prevent reperfusion injury following coronary bypass surgery and the use of retrograde cardioplegia for myocardial protection during cardiac surgery need to be further investigated in clinical trials.

There is no question that the coronary venous pressures seen in patients treated with SRP during ischemia in the LAD coronary artery distribution are not nearly as adequate as the pressures seen in animal models such as in the canine. The probable explanation for that is the more pronounced Thebesian flow in the human compared to the dog. However, different catheter operation and mechanisms are currently being investigated to more consistently increase the coronary venous pressures during SRP in order to overcome this problem, and hopefully these modifications will enhance the efficacy of this technique.

Another area in which catheter technology and research will be of great importance is concerning the efficacy of SRP during ischemia of the left circumflex and right coronary artery perfusion territories. Because the coronary sinus tributaries draining these regions are more proximal to the coronary sinus ostium, they are also more difficult to retroperfuse. In this latter condition, coronary sinus catheter stability might present a problem. On the other hand, it is possible that in many patients the rich epicardial veno-venous connections of regional veins draining blood from the three major coronary artery perfusion beds may allow for perfusion of these territories even with the SRP catheter positioned in the great cardiac vein. In at least two patients with acute inferior wall myocardial infarction in whom SRP was used, there was evidence of beneficial effects documented by improved ECG signs of ischemia and wall motion[94]. Nevertheless, these are just anedoctal findings which need to be corroborated by well designed research protocols.

SRP has also been effective in a few patients who developed cardiogenic shock during abrupt coronary artery closure following PTCA. Again, it is speculated that SRP might more effectively perfuse the myocardium in patients with severe hypotension or shock because of limited coronary arterial inflow under these circumstances, and therefore less competitive antegrade flow. It is also possible that in such situations, when LV end:diastolic pressures are usually very high, that LV unloading devices such as intra-aortic balloon counterpulsation could be particularly efficacious when combined with a technique which primarily provides myocardial oxygen supply, such as SRP. It is not known, however, to what extent SRP alone will provide systemic support in hemodynamically compromised patients[95]. Further studies are needed to answer some of these questions.

We believe that SRP of cooled arterial blood, which can rapidly reduce myocardial temperatures and therefore significantly delay irreversible myocardial ischemic changes, is a potentially useful variation of the SRP technique. Hypothermic SRP may be of clinical significance in patients who develop abrupt coronary artery occlusion in the catheterization laboratory as a complication of angioplasty, and who have to undergo emergent surgical revascularization. Futhermore, recent studies using this technique to preserve graft viability in a canine model of orthotopic heart transplantation have indicated that additional hypothermic coronary sinus perfusion of a cold electrolyte solution during implantation of the preserved heart provided better graft viability compared to conventional methods[96].

Coronary sinus interventions, particularly SRP and drug retroinfusion, also need to be investigated in larger studies in patients with rest angina unresponsive to medical therapy, Although these patients usually benefit from nonsurgical or surgical revascularization, it may be possible to control symptoms and reduce myocardial ischemia with SRP as previously suggested[29], allowing time for spontaneous or drug-induced relief of the basic mechanism responsible for the ischemic episodes. Other potential applications of SRP includes patients with acute myocardial infarction in whom early reperfusion strategies cannot be readily applied, such as in cases of acute ischemia or infarction during noncardiac surgery or even in patients with early graft closure following coronary bypass surgery.

In respect to the use of retrograde cardioplegia and PICSO following bypass surgery, it is crucial to improve methods of myocardial protection, particularly in this age and era where surgical candidates are getting older and sicker and therefore require more complex surgical treatments. In many cases, these high-risk patients cannot tolerate additional myocardial damage during or immediately after bypass surgery, which will be translated into an increased morbidity and mortality rates.

On the other hand, as pointed out by Mohl[97], we must also be aware of what coronary sinus interventions cannot do, and that is to compete with reperfusion in cases where myocardial perfusion is suddenly impaired and rapid reestablishment of antegrade flow is needed. Although coronary sinus interventions have been extensively studied in animal models and initial clinical studies look promising, there is still much needed clinical experience with most of these techniques as well as more research and development, particularly in the

area of catheter technology, before some of these interventions become more widely accepted in clinical practice.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the secretarial assistance of Ron Arzaga and the editorial assistance of Jeanne Bloom. They also thank Rosa Goldsmith for preparing the illustrations.

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