Austria.

DECADES THREE introduced have developed. New technologies and techniques have allowed considerable progress in this area and we are now challenged with answering the provocative question: Do these recent strides demonstrate a realistic clinical potential for CSI?

**History of coronary sinus interventions.** As early as 1703 Adam Christian Thebesius reported on his observations about the coronary venous system in his thesis "De Circulo Sanguine in Corde": "Thank God for the ingenious device of coronary ventricular channels, which relieve the myocardium from the coronary blood and thus prevent accumulations of interstitial fluid." The drainage pathways so described were later named the Thebesian system, documenting the significance of the findings of the 17th century researcher, who contributed significantly to the understanding of the essential nature and mechanism of the coronary circulation.

In subsequent years little was added to this basic understanding of the coronary venous physiology of the human myocardium. It was only in the late 1800's that the rediscovery of the anatomy of the coronary venous system by Langer stimulated further research endeavors, most notably those of F. H. Pratt, which provided the basis for today's concepts of CSI. In 1893 Pratt published his experimental results on retroperfusion of arterial blood in isolated dog and cat hearts with the conclusion that "the nutrition of the mammalian heart is not totally dependent on the coronary arteries." His and all subsequent findings on retroperfusion have continued to fascinate generations of researchers, and have introduced a new era in coronary sinus research, which today again appears to be on the threshold of allowing application in clinical trials.

Today CSIs are generally understood to be methods of temporary protection of ischemic myocardium via the coronary venous system and include retroinfusion of cardioplegia during cardiac arrest in surgery, retroperfusion of arterial blood in settings of myocardial infarction (synchronized retroperfusion or SRP), retroperfusion of pharmaceutical agents, and manipulations of venous blood drainage by pressure-controlled intermittent coronary sinus occlusion (PICS0) are just beginning to be tried in clinical treatment aimed at extending myocardial viability during severe but reversible ischemic injury.

(1) The coronary venous vasculature remains unaffected by the atherosclerotic disease process, which often causes severe coronary artery obstruction and may jeopardize regional myocardium deprived of essential perfusion and substrates. All of the several categories of CSIs have been extensively studied in the laboratory. Surgical retroinfusion of cardioplegia is already being applied in substantial patient subsets. SRP and PICS0 are just beginning to be tried in clinical treatment aimed at extending myocardial viability during severe but reversible ischemic injury.

(2) The coronary venous vasculature is a dense meshwork with numerous interconnections, offering an approach for retrograde delivery that can be accomplished by increasing coronary vein outflow impedance (PICS0) and/or provision of supplemental reverse flow (SRP).

**The wrong goal and approach to permanent retroperfusion.** Some 40 years ago, and preceding many of the enormous advances associated with modern cardiovascular medicine, major experimental studies were performed to evaluate whether coronary sinus occlusion and arterIALIZATION represented an effective treatment for myocardial ischemia. The names of investigators are familiar and include Drs. Gregg, Eckstein, and Beck. The early successful studies eventually lead to the application of the Beck II surgical retroperfusion procedure in about 200 patients with coronary artery disease. Beck's procedure involved shunting of blood from the aorta into the coronary...
FIGURE 1. Schematic comparison between the three CSIs that are today under clinical consideration: SRP, PICS0, and retroinfusion in the normal working and arrested heart. During SRP arterial blood is shunted from the femoral artery into a pump console and pumped during diastole into the coronary sinus. Pump action is triggered by the electrocardiogram. During PICS0 the coronary sinus pressure triggers the balloon occlusions (closed-loop control). Retroinfusion of pharmaceutical agents in the working heart can be performed by use of timed coronary sinus occlusion, PICS0, or SRP. In the arrested heart cardioplegia is delivered under constant infusion with a perfusion pressure between 20 and 40 mm Hg.

sinus, which was subsequently ligated to elevate pressure in the coronary veins and thus ensure delivery of arterial blood into ischemic zones of the left ventricle. Early experimental data and clinical application appeared promising in that they documented temporary relief of symptoms. However, the permanent nonphysiologic pressure increase in the coronary venous system, along with regional arterial underperfusion due to impedance of normal coronary arterial flow, gave rise to excessive mortality and severe derangements, such as myocardial hemorrhage and edema. Coupled with a limited understanding of mechanisms, the observed detrimental effects eventually resulted in disenchantment with the surgical retroperfusion procedure. Some attribute the consequent temporary “demise” of retroperfusion concept to the presumed but apparently wrong objective of permanent high-pressure arterialization of the coronary veins, while others simply blamed the insufficiently advanced technology and poor means of assessment of the treatment.

One could still hypothesize that an improved mode of permanent arterialization would be useful in the specific setting of generalized severe diffuse atherosclerosis of coronary arteries, i.e., that this might prevent deterioration of myocardial viability. Yet, in most of clinical settings requiring treatment the extent to which the coronary arteries of the distribution areas are diseased is variable, and hence, in most instances permanent retroperfusion leads to severe changes in areas where “normal” or relatively satisfactory residual perfusion prevails.13

Today’s concepts of CSI for myocardial protection
Synchronized retroperfusion. While it was the purpose of Beck’s operation to provide for permanent treatment of underperfusion in patients with chronically diffuse coro-

Vol. 77, No. 1, January 1988

nary heart disease, Meeraum et al.5 with their development of the SRP technique have defined a new sphere of application for CSI, namely temporary support to acutely jeopardized ischemic myocardium. SRP, that is retroperfusion of arterial blood synchronized to diastole allowing for normal physiologic coronary venous drain-
age in systole, has undergone a decade of detailed evaluation. Extensive experimental trials have shown that this technique, when performed during coronary artery occlusion, improves myocardial metabolism and left ventricular function, favorably redistributes blood flow toward the endocardium, and reduces the ischemic zone and infarct size. A recent clinical trial of SRP by Gore et al. performed in patients with unstable angina pectoris documented that SRP is a feasible and safe intervention that may increase the likelihood of recovery from a variety of acute myocardial ischemic events.

The mechanism of action of SRP is assumed to be retroperfusion of arterial blood and substrate delivery into the ischemic zone. Methods for validating the presumed mechanisms have included microsphere and dye solution studies, venograms, and two-dimensional echocardiographic contrast studies. There is, however, persistent doubt as to whether the retroperfusion pressures during these studies are equal to those during “normal” SRP applications. Chang et al. recently reported that a further mechanism of SRP may be washout.

Another interesting modality was studied by Haendchen et al., who applied great cardiac vein hypothermic retroperfusion for 2½ hr in dogs during a 3 hr occlusion of the left anterior descending artery, followed by 7 days of reperfusion. Retroperfusion resulted in significant improvements in postreperfusion recovery of cardiac function.

A further extension of SRP was reported by Meerbaum et al., who studied intravenous vs coronary venous retroinfusion of streptokinase. The clot was lysed much earlier in the retroinfused group than in the intravenous group.

From the evidence presented it may be concluded that retroperfusion methods may have the potential to provide temporary retrograde circulatory support by delivering oxygen and substrates and pharmacologic treatment to jeopardized myocardium. The effect of SRP at the microcirculatory level is, however, still ill-defined, and there is still the problem of venous shunting, which may severely impair delivery of the retroperfusate to the zones of interest.

Pressure-controlled intermittent coronary sinus occlusion. Proceeding on the assumption that the reported benefit of Beck’s operation with respect to relief of ischemic symptoms may have been mainly due to changes in pressure and flow in the microcirculation, and only to a lesser extent on oxygenation, in 1984 our group developed PICS, aimed at protection of ischemic myocardium.

This technique does not use arterialization or synchronization to diastole. Instead, PICS’s effective-ness appears to be attributable in part to residual substrate and oxygen in the coronary venous blood spontaneously forced into the ischemic zone microcirculation (redistribution phase). In addition, PICS reestablishes flow currents that promote washout of accumulated toxic wastes in the ischemic area (washout phase). By analogy one might say that the venous blood during PICS clears the ischemic zone like clear running water cleans out a dirty sponge.

To allow optimal effectiveness of the technique it has to be taken into account that temporary intermittent occlusion of the coronary sinus can only be effective within a certain physiologic range delimited by the extremes of either too long or too short an occlusion phase. The occlusion versus release phases of the cycle are adjusted as indicated by the changes observed in the coronary sinus occlusion pressure. That is, the coronary sinus is occluded until coronary sinus pressure reaches a certain percentage of its (predicted) plateau. Coronary sinus occlusion is then released, facilitating venous drainage and a return to baseline pressure. This timing mechanism may be effective in avoiding counterproductive effects on antegrade flow and subsequent endothelial damage, hemorrhaging, and edema formation (figure 2).

In numerous experimental studies PICS has been shown to reduce infarct size and improve regional ischemic function in the setting of acute myocardial injury, i.e., coronary artery stenosis, infarction, and reperfusion. Recent applications of PICS in man appear to support the experimental benefit of the intervention. In a randomized trial of 30 patients undergoing coronary artery bypass grafting, two-dimensional echocardiographic measurements were used to evaluate the effect of PICSO on global and regional myocardial function, expressed as (sectional and segmental) percent fractional area change. PICSO was started shortly after aortic declamping and continued for 1 hr during the early reperfusion phase. Control subjects underwent reperfusion alone. The between-group differences in regional and global wall motion showed a trend indicating that PICS maintained myocardial function better than reperfusion alone, and may therefore ameliorate reperfusion-induced myocardial injury.

Comparison of SRP and PICS. Although apparently SRP and PICS are based on two different concepts, both were able to overcome the essential drawback of the early-day coronary sinus approaches, i.e., with both techniques it is possible to prevent the counterproductive sequelae observed with permanent interference with venous drainage.
What distinguishes SRP from PICSO is that they are related to two different schools of thought about primary mechanisms CSIs. Thus, the rationale for PICSO holds that the beneficial effects are mainly based on a forced redistribution of venous blood flow in the coronary beds. In contrast, the rationale for retroperfusion maintains that its benefits primarily result from retrograde substrate and oxygen delivery with the retroperfused arterial blood. One thing they have in common, however, is that both their effects appear to be related to washout.17, 21

The concept of a potential contribution of myocardial metabolite washout to improved tissue salvage and improved function during acute ischemia or evolving myocardial infarction is consistent with reports from Murry et al.25 and Neely and Grotyohann.26 These authors found a relationship between cell integrity, viability, functional recovery, and catabolite accumulation during ischemia and reperfusion. If adequately validated, enhanced myocardial washout and redistribution could support prior physiologic studies implicating accumulation of toxic metabolites in ischemic injury. However, further studies are warranted to more conclusively establish the presumed washout mechanism of both PICSO and SRP. What is known is that when acute ischemia oxidative metabolism ceases, citrate and ATP levels fall and glycolysis is stimulated. During prolonged periods of ischemia accumulated products (i.e., protons, lactate etc.) inhibit glycolysis.27 This is certainly only one example of the effect of an accumulation of metabolites and only one possible explanation of why washout of these products may improve function. Various techniques, such as xenon dilution and microspheres or blood density measurements,28, 29 have been used to measure washout. In the instance of PICSO, washout was quantified with a method, described by Kenner et al.,28 that measures arteriovenous differences of blood density gradients in the circulation. Figure 3 shows that there is significant correlation between washout, measured as the arteriovenous blood density gradient change,21, 28 and coronary sinus pressure.

As illustrated in figure 2, PICSO induces a decrease in arterial flow during occlusion that has to be compensated for by allowing an adequate hyperemic response during coronary sinus release. To optimize the occlusion vs release cycles we are currently evaluating these response patterns using a closed-loop model.

It can be speculated that SRP would induce similar responses of coronary sinus pressure and hence similar effects on arterial inflow. Recent studies on SRP by Smalling30 and Beatt et al.31 seem to support the idea that it would hence be equally important for SRP to optimize coronary sinus pressure and flow rates. The additional oxygen delivery with retroperfusion further complicates attempts at comparison of the effects of different coronary sinus interventions in the normal working heart against each other. However, in general

**FIGURE 2.** Venous pressure (CSP) and coronary artery inflow measured electromagnetically in the circumflex artery (CX artery mean flow) during intermittent coronary sinus occlusion. The minimum flow (Fmin) occurs when the systolic pressure plateau is reached (i.e., 95% of the predicted plateau value). The maximum flow (Fmax) in the coronary artery is used for the development of an algorithm for coronary sinus release phase to determine closed-loop control during PICSO. Prolonged occlusions or inadequate release phases produce a counterproductive effect on arterial inflow (which stays low throughout the occlusion and beyond the coronary sinus pressure plateau).

**FIGURE 3.** Relationship between washout, measured as the arteriovenous density gradient change, and coronary sinus pressure. (Modified from Moser et al., as published in: Mohl W, Wolner E, Glogar D, editors: The coronary sinus. Darmstadt, 1984, Steinkopff Verlag, p 505).
it may be said that the individual reports on the effectiveness of the coronary sinus interventions, as far as they allow comparison, suggest that SRP and PICSO are of equal benefit.

An actual comparison between different retroperfusion modalities was studied by Zalewski et al. They reported of a superiority of retroperfusion of arterial blood over retroperfusion of venous blood and intermittent coronary sinus occlusion (ICSO). However, the technique of time-dependent ICSO, which does not use continuously monitored coronary sinus pressure for the adjustment of the occlusion vs release cycles, is not compatible with that of pressure-dependent PICSO, and hence these negative findings do not allow extrapolation with respect to the effectiveness of PICSO. Unfortunately, in the literature the terms ICSO and PICSO have been used somewhat synonymously, which in part accounts for the fact that attempts by other research groups to corroborate the beneficial effects of PICSO have produced variable results. While several studies supported the reported benefit of PICSO, two studies did not confirm the positive results. In the negative studies the investigators used either no monitoring of coronary sinus pressure, or used non-physiologic cycle lengths of 30 sec of occlusion and 30 sec of release.

Owing to the fact that I am personally involved in the development of PICSO, I will not attempt to make a conclusive statement as to which technique is superior. It is assumed that according to the data provided the reader will make an individual judgment. The general lack of studies comparing SRP and PICSO appears to be due to the fact that the presumed additional beneficial effect of oxygenation with SRP can only be established via a vis the effect of PICSO if all three SRP variables, i.e., coronary sinus pressure, coronary sinus blood flow, and external retroperfusion flow, are controlled.

Due to the generally ready access to ischemic myocardium via the coronary venous system and the coronary sinus, techniques such as SRP and PICSO might indeed introduce a new useful modality of support as part of interventional cardiology. At present, however, too many questions are yet in need of clarification: Is the human anatomy of the coronary venous system comparable to that of the laboratory animal? Can myocardial uptake of oxygen and substrates as observed in the laboratory animal be extrapolated to uptake in humans? Will coronary venous reflexes in the conscious, responsive patient alter the hemodynamic response pattern? Which coronary sinus interventions are most efficacious in settings of acute myocardial infarction? Are our current means of assessment of the effectiveness of the treatment adequate? Are these mechanisms primarily related to resupply and oxygenation via coronary veins, or rather to alteration in myocardial blood circulation due to increased impedance to coronary venous drainage?

Retroinfusion techniques. The third coronary sinus technique is the retroinfusion of pharmaceutical agents and cardioplegic solutions. (See figure 1 for a schematic of the three coronary sinus techniques.) Basically there are two types of retroinfusion via the coronary sinus. One is applied during cardiac arrest in open heart surgery, providing a more homogeneous occlusion. The other, with a mechanism similar to that of SRP, is used in the normal working heart. The concept of retroinfusion has regained great interest only in recent years. The finding of Meerbaum et al. of a significantly earlier lysis with coronary venous streptokinase appears particularly interesting because it indicates that combination of CSIs with conventional therapies may provide enhanced treatment.

Karagueuzian, Povzhitkov, Otsu, and Meerbaum and their colleagues all recently reported a superiority of retroinfusion of pharmacologic agents over conventional methods. However, careful evaluation will have to be used to ascertain whether the retroinfusate/retroperfusate, or the redistributed antegrade flow induced by restricting venous flow, is actually delivered to the zones of interest.

Retroinfusion of cardioplegic solutions is distinguishable from SRP or PICSO in that it is performed in the nonworking heart. Its specific advantages include minimal interference with the surgical procedure, avoidance of trauma to the coronary arteries, and a more uniform distribution of cardioplegia. Furthermore, monitoring of flow rates and pressures during cardioplegic arrest should enhance prevention of damage to endothelial cells. Whether it is continuous retrograde cardioplegia, pulsatile retrograde cardioplegia, or antegrade cardioplegia in combination with PICSO, each of these modalities has been found superior to conventional cardioplegia in protecting myocardium in experimental studies with coronary artery occlusion and in an increasing number of clinical applications in patients with severe coronary heart disease, where antegrade cardioplegia is distributed inhomogeneously. However, these positive reports have not remained unchallenged, and further studies are hence warranted to firmly establish these techniques as viable approaches.

Benefits vs risks of CSIs. At this stage of development CSIs appear to have two primary clinically useful
effects: They delay lethal cell injury, and they protect against reperfusion injury.\textsuperscript{24}

We are, however, also aware of what CSIs cannot do. In the working heart CSIs will never be able to compete with reperfusion techniques. They are also unlikely to be beneficial in settings of "demand ischemia," in which perfusion is suddenly impaired.

With due respect to these limitations the fact remains that there are still certain subsets of patients who would definitely benefit from the application of CSI to bridge those periods of myocardial jeopardy in which conventional techniques of interventional cardiology and cardiac surgery still fail to provide relief.

In the setting of myocardial infarction, the fact that reperfusion techniques may result in reperfusion injury even in patients in whom thrombolysis or angioplasty is successful suggest that there is an adjunct role for CSI to further reduce myocardial damage. Especially in patients who do not qualify for thrombolytic therapy, CSIs, with their potential to delay cell necrosis and to make the ischemic area receptive to reflow, may be very useful for the salvage of additional myocardium.

The same holds true for the setting of unstable angina in which there are still subsets of patients in whom medical therapy (β-blockers, calcium antagonists, and nitrates, including intravenous nitroglycerine) fails to control symptoms.

A further very promising modality is retroinfusion of pharmacologic substances into the working heart to influence refractory arrhythmias or to provide additional protection of the ischemic area.

Finally, in the setting of cardiac surgery, it appears that retrograde perfusion may offer an alternative method for overcoming nonhomogeneous distribution and protection. Furthermore, the fact that the surgeon is confronted with an increasingly ill patient population calls for adjunct measures to prevent perioperative myocardial damage. High-risk patients with severe coronary artery disease undergoing complex cardiac surgery are highly likely to benefit from retroinfusion of cardioplegia and additional myocardial protection during the reperfusion period.

Now that we are on the threshold of taking these methods to the clinical trial it is essential to also discuss potential risks that may be associated with CSIs. One of the risk factors relates to catheterization of the coronary sinus. Guerci et al.\textsuperscript{46} recently reported damage to endothelial layers, structures of the wall, and thrombosis. It has to be taken into consideration, however, that in this experimental series no anticoagulants were given. A second area of concern is that thrombolytic therapy or anticoagulation together with elevated pressures in the coronary sinus may cause structural damage or arrhythmias. Our own experimental studies and clinical experience with applications of PICSO during bypass surgery have yielded no evidence of this. A third and maybe more important risk factor is that of hazardous pressure elevations in the coronary venous system to 50 mm Hg or more, as has been reported by authors using retroperfusion.\textsuperscript{47, 48} Our own studies with PICSO, have, however, indicated that pressures may increase to 50 mm Hg or even higher without ensuing damage or trauma to the coronary sinus or veins. Care must be taken, however, to avoid prolonged occlusion, which has been reported to cause damage or arrhythmias.

Generally speaking, as was the experience with intra-aortic balloon pumping or other accepted new modes of treatment, clinical application of a new method during the learning phase always imposes additional risks on the patient. The question we are faced with is: Is it legitimate to clinically test an intervention about which there are unanswered questions? One answer is given by Dwight Harken, who writes in his article "To Beck and Back":\textsuperscript{49} "A device is safe when it is safer than the disease it corrects and it is the best available." Taking this tenet as our ethical guideline it should be possible to enter the clinical stage, and to attain more complete insight into the mechanisms of CSIs and their clinical significance. Coming trials will require a maximum of scientific integrity, which should allow the investigator to determine whether extrapolation of animal results to humans is possible, and whether observed benefits warrant the effort. Yet, not to have tried at all for the sake of being unchallenged might expose humans to tragic errors of omission or, as Dr. Beck, the doyen of coronary sinus interventions, liked to say\textsuperscript{49} "Prophesy without experience is a dangerous philosophy."

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Vol. 77, No. 1, January 1988

11


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