Progress in
Coronary Sinus Interventions

CSI —
A new Approach to Interventional Cardiology

Edited by W. Mohl, D. Faxon, E. Wolner

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Contents

Editorial

Increasingly, cardiologists are using the coronary sinus as an access route for the protection of the myocardium. To bring the latest information on the progress of research findings gathered with respect to coronary sinus intervention to a growing number of scientists world-wide, a new series has been initiated, of which this forms the first volume.
The series is edited by the International Working Group on Coronary Sinus Interventions (WCSI), which we have recently established to serve the interests of the patient by continuous reassessment of this new method, to ensure maximum safety in its application in human settings. Experts in coronary sinus interventions from all over the world have combined to share their data and subject their research to further evaluation.
Progress in Coronary Sinus Interventions thus forms a series which will provide the reader with information on the advances made in research on this subject, and will contribute to an enhanced understanding of the nature of the coronary circulation, its anatomy, pathology and pathophysiology. The publication of these research data will establish a context in which new techniques can be evaluated within the framework of conventional methods and therapeutic approaches in interventional cardiology.
The editors have set themselves the objective of presenting the latest information in a clear, concise and readable form, with emphasis on the most essential parameters, for example the state of the art technology involved in the coronary sinus approach.
This first volume covers all relevant aspects which will serve as a basis for discussion for clinical studies with respect to synchronized retroperfusion, retroinfusion of pharmaceutical agents, and pressure controlled intermittent coronary sinus occlusion.
Progress in CSI is intended for those who are active in the field of coronary sinus interventions and coronary surgery, for whom the challenge of finding an effective treatment for cardiac disease is growing even more demanding.
Since this series owes its existence to team-work, we would like to thank all our colleagues around the world for their encouragement and continuing support in our mutual aim of establishing the route via the coronary sinus as a viable approach.

January 1986

W. Mohl
D. Faxon
E. Wolner

Report of the international working group on coronary sinus interventions

W. Mohl, D. Faxon, D. Glogar, J. M. Gore, A. Jacobs, D. Mai, S. Meerbaum, M. Moser, A. Juhasz-Nagy, C. Punzengruber, G. Raberger, A. Roberts, H. Tritthart, E. Winters, and E. Wolner

This communication constitutes a report on the first meeting of the Ad Hoc Committee on Coronary Sinus Interventions held in Rust, Austria, December 2–5, 1984 (Fig. 1). This committee was proposed during the 1st International Symposium on the Coronary Sinus, which took place in Vienna in February, 1984 (5), with the purpose of facilitating more direct and detailed discussions of current issues in the field of interventions via the coronary sinus. In a way, this committee constitutes the second generation of investigators who focus their research work on the coronary sinus and its potential as a means of protecting jeopardized myocardium during acute ischemic syndromes as well as during

Fig. 1. The Working Group photographed in Rust, Austria.

cardiac surgery. In the pioneering era of some 40 years ago Beck and his colleagues demonstrated the feasibility of the coronary sinus approach; long-term results were, however, disappointing. Renewed studies and more refined approaches have provided new information and suggest that retrograde techniques have the potential of providing an important supplement to those methods that have so far been used in the treatment of myocardial ischemic syndromes. Although definite benefits of coronary venous interventions have been demonstrated in the laboratory, clinical experience has been rather limited and a significant number of questions has remained open. The International Working Group on Coronary Sinus Interventions hopes to serve as a permanent panel for the promotion of the exchange of information and critical evaluations of both clinical and research endeavours in this challenging and expanding field.

Background

Since the time when retroperfusion was initiated by Claude Beck (1) in the form of a permanent surgical arterialization of the coronary sinus with subsequent coronary sinus ligation, there have been significant changes in both the aims and the methodology of coronary venous treatment. Two basically new forms of myocardial protection via the coronary veins were developed in the 1970s: 1) synchronized diastolic retroperfusion with arterial blood (SRP) and 2) pressure controlled intermittent coronary sinus occlusion (PICSO). Both these techniques feature phased pulsatile systems, developed with the help of modern technology and specifically designed to avoid prolonged periods of interference with coronary venous drainage and build-up of hazardous elevations of coronary venous pressure, which can lead to significant vascular trauma, myocardial edema, and irreversible tissue damage.

Principles of retroperfusion

The principles of coronary sinus interventions are inevitably linked with the specific patterns of the underlying coronary venous anatomy and pathophysiology. In the left heart, approximately 70% of the coronary blood flow drains through the coronary sinus while the rest drains via smaller cardiac veins, including the Thebesian system. The total number of myocardial veins and venules generally exceeds the number of coronary arteries; this intricate and vast meshwork disposes of the intrinsic potential of facilitating a more homogeneous distribution of retrograde flow to underperfused myocardial regions subserved by obstructed coronary arteries. Venous valves and numerous shunts, including arterio-venous, veno-venous, and veno-luminal vessels, may also play a role in determining the efficacy of retroperfusion techniques.

The coronary venous drainage consists of a phasic high flow, low pressure circulation which essentially empties the network of small coronary venules during the heart's systole after having been filled by the arterial vasculature during diastole. To avoid the problems caused by undue interference with systolic physiologic coronary venous drainage, retrograde treatments take advantage of minimal antegrade myocardial efflux in diastole. In addition, coronary venous compliance and capacity will also affect the therapeutic effectiveness of retroperfusion techniques.

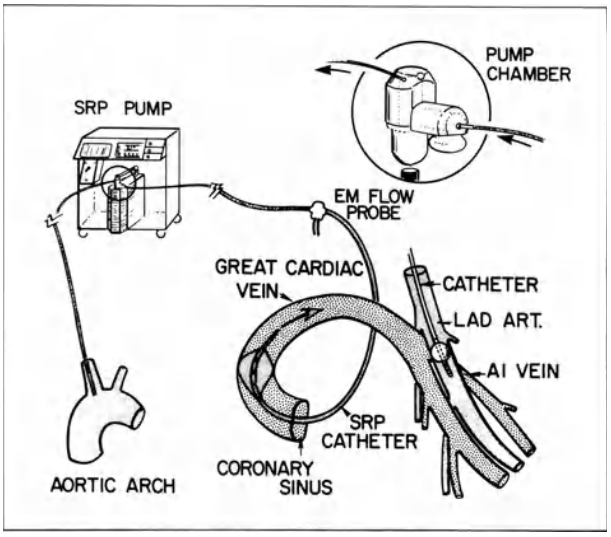

Fig. 2. Schematic of SRP pump and auto-inflatable balloo catheter. Pump reservoir and chamber are shown in insert. Reproduced from Drury et al. in (5), p. 348.

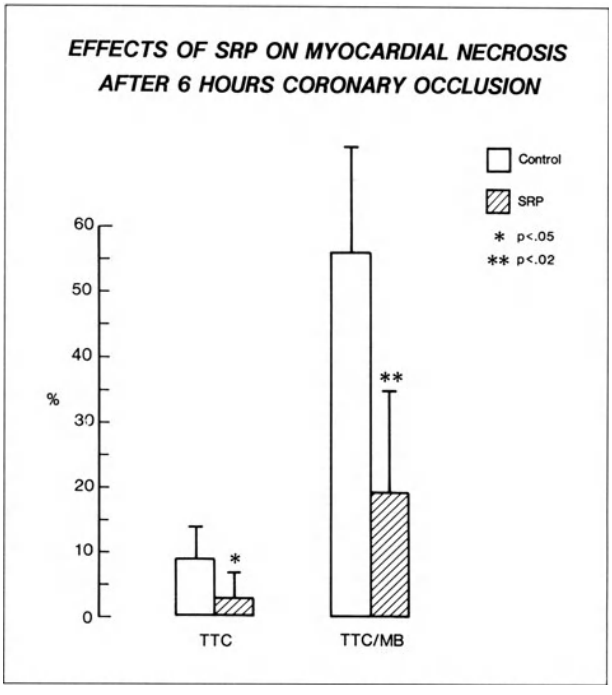

Fig. 3. Comparison of extent of myocardial necrosis (triphenyl tetrazolium chloride) expressed both as a percentage of left ventricle (TTC) and as a percentage of area at risk (TTC/MB). Reproduced from Drury et al. in (5), p. 352.

Synchronized retroperfusion

Synchronized retroperfusion (SRP) was developed during the early 1970s at the Cedars-Sinai Medical Center (Los Angeles, California) (3). In the SRP system, blood from a suitable arterial site is pumped during cardiac diastole into the regional coronary veins ad-

joining the experimentally obstructed coronary arteries (Fig. 2). This method facilitates coronary venous drainage during cardiac systole and minimizes vascular congestion, myocardial edema and hemorrhage. The amount of arterial blood retroperfused in closed chest dog studies ranged up to 100 ml/min, and special measurements indicated that the regional coronary venous blood pressure during SRP could be kept down to an average of 30–40 mm Hg with systolic peaks not exceeding 60 mm Hg, which, according to the experience of various investigators, constitutes an adequate safety threshold. SRP promptly and significantly improved acutely ischemic myocardial function and significantly decreased infarct size (Figs. 3 and 4). The efficacy of SRP has subsequently been corroborated by various investigators in canine and primate models. Recently a group at the University of Massachussetts extended SRP studies over a 20 hour period and found them to have no adverse effects on blood components or chemistries, provided that activated clotting time was maintained at 2 to 2.5 times baseline. By now moderate myocardial hypothermia and cardioactive drug retroinfusions have also been shown to further enhance SRP effectiveness. A study of SRP combined with streptokinase coronary venous infusion indicated the feasibility of retrogradely lysing a coronary artery thrombus. Most recently, retrograde coronary venous administration of antiarrhythmic agents has been shown to be another interesting modality. Evidence and interpretation of SRP data suggest that

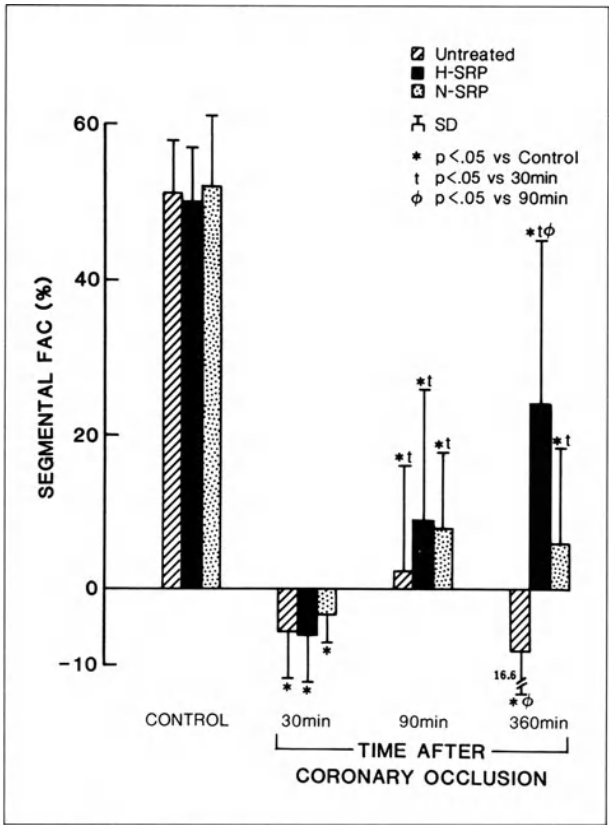

Fig. 4. Effects of retroperfusion on regional LV function. FAC = intraluminal systolic fractional area change, SD = standard deviation. Other abbreviations as in Fig. 3. Reproduced from Haendchen et al. in (5), p. 398.

oxygen delivery in combination with improved retrograde perfusion as well as washout from acutely ischemic zones are the primary mechanisms of this coronary venous intervention.

Pressure controlled intermittent coronary sinus occlusion (PICSO)

PICSO is a concept that was developed at the 2nd Surgical Department of the University of Vienna in the late 1970s (4). So far PICSO has been tested in 65 animals and 15 humans. The idea to develop a pressure controlled CS occlusion stems from observations which suggested that coronary inflow and distribution could be influenced by coronary venous manipulations, and the assumption that the observed beneficial effects of retroperfusion in the case of myocardial ischemia may largely be due to changes in pressure and flow within the coronary microcirculation. Intermittent balloon blockade of the coronary sinus is assumed to redistribute blood from non-ischemic zones to underperfused zones, which results in an increase in the venous blood circulation in the ischemic zone and a washout of plasma-like fluid and toxic metabolites from the jeopardized myocardium (Fig. 5). Experimental studies have indicated that PICSO significantly reduces infarct size (Fig. 7) and improves ischemic wall motion (Fig. 6).
The alternate phasing of the coronary sinus occlusion is controlled consistently with the coronary sinus pressure that develops during its occlusion. The systolic blood pressure in the occluded coronary sinus rises beat by beat over a period of a few seconds until it reaches a plateau, which is thought to be an index for optimally controlled coronary sinus occlusion. The coronary sinus ballon is intermittently deflated for a period of 2–5 seconds, which allows for adequate washout. This phased timing has to be controlled throughout the intervention because of changes occurring in pressure rise. Because of the brevity of individual coronary sinus occlusion, it is not believed necessary to limit coronary veinous pressure to a level consistent with longer periods of coronary veinous obstruction or retrograde pumping. On the other hand, it was found to be important to en-

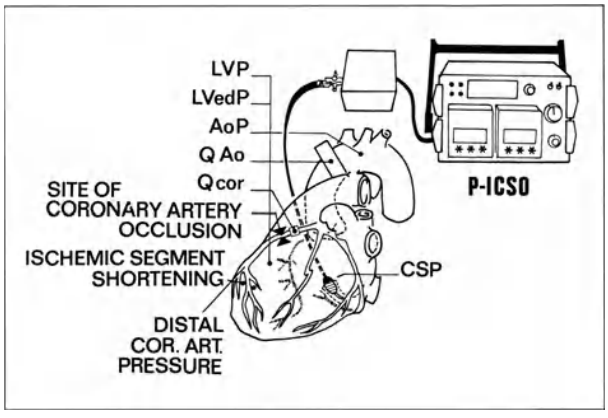

Fig. 5. Schematic illustration of the experimental preparation of open chest dogs. Coronary sinus pressure (CSP) is monitored through the coronary sinus balloon occlusion catheter, which is connected to the pumping system. The latter automatically triggers balloon inflation and deflation for pressure controlled intermittent coronary sinus occlusion (P-ICSO). AoP = aortic pressure; COR. ART. = coronary artery; LVedP = left ventricular end-distolic pressure; LVP = left ventricular pressure; Q Ao = aortic flow: Q cor = left anterior descending coronary artery flow. Reproduced from Mohl W et al (1985) JACC Vol 5, No 4: 939–947.

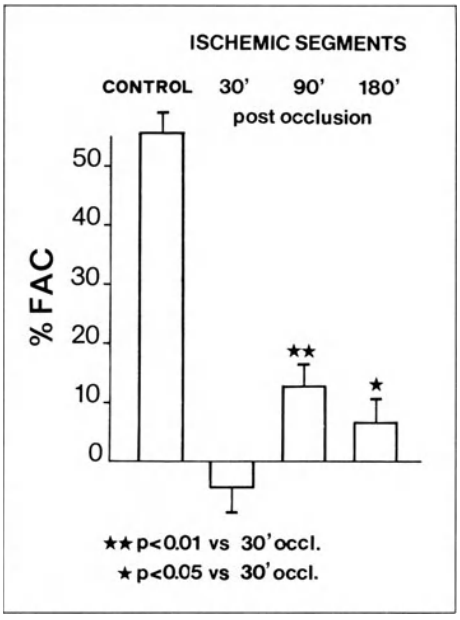

Fig. 6. Two-dimensional echocardiographic measurements in closed chest dogs. Effects of pressure controlled intermittent coronary sinus occlusion (PICSO) on segmental systolic fractional area change (%FAC) in all ischemic ventricular segments showing less than 5% wall thickening 30 minutes after left anterior descending coronary artery occlusion (Occ). Reproduced from Mohl W et al (1985) JACC Vol 5, No 4: 939–947.

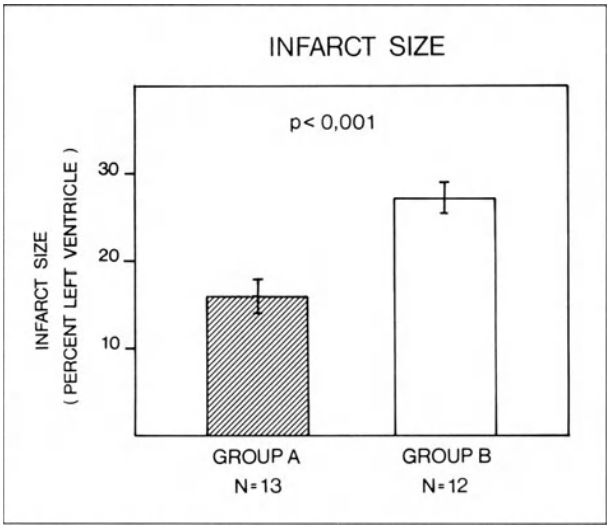

Fig. 7. Infarct size (percent left ventricle). Reproduced from Mohl W et al (1984) Am J Cardiol 53: 923–928.

sure exact monitoring of PICSO timing and phasing, because otherwise this intervention might prove counterproductive and actually limit arterial inflow. Furthermore it has been found desirable to monitor the coronary sinus pressure with regard to potential diagnostic information derived from coronary sinus pressure-flow relations.

Retroinfusion

Retroinfusion of pharmaceutical agents can be combined with either SRP or PICSO in the beating, ischemic heart or by continuous retrograde infusion such as currently per-

formed with cardioplegic solutions during open heart surgery (7). In its latter applications, a cannulation of the coronary sinus with a purse-string suture is easily accomplished through the right atrium near the inferior vena cava, and retrograde cardioplegia is delivered without disturbing the operating field. The special anatomy of the venous vasculature permits a more uniform protection of the heart, especially in the presence of hypertrophic or atherosclerotic coronary lesions. In several experimental and clinical studies retrograde cardioplegia has been beneficial in the presence of left myocardial edema and has been associated with a postoperative increase in left ventricular function (Fig. 8).

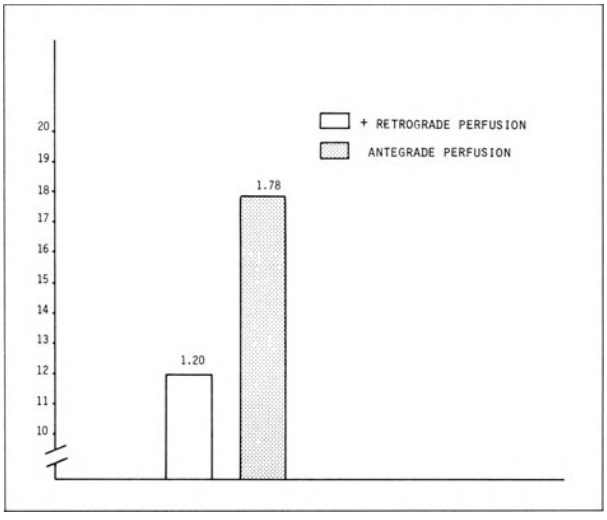

Fig. 8. Semi-quantitative ultrastructural changes. Reproduced from Walter et al. in (5), p 289.

Instrumentation and quality control

Any new method or device must, or course, be demonstrated to be safe and fail-safe. Retrograde coronary venous interventions may produce a significant disturbance of the normal coronary venous drainage, which could be disadvantageous or even hazardous. The duration and pressure as well as the flow in the coronary veins should therefore be well monitored. While the wall of the coronary sinus generally resembles that of the great collecting peripheral veins, pressure on coronary sinus receptors and nerve endings embedded in the connective tissue may also play a role in the so-called coronary sinus "reflex" mechanisms. Based upon experience, catheterization of the ostium of the coronary sinus should prove successful in 80–90% of all cases. Nevertheless, knowledge of the variability of the coronary venous anatomy, as well as of the functional variations in the coronary venous system, especially during disease, is an important prerequisite for rational coronary venous manipulations.

Ultimately, retrograde coronary venous systems will be used by less experienced and knowledgeable medical personnel. Hence, it is preferable to design the system with auto-

matic features built in wherever possible to assure safety. Currently, safety considerations for either SRP or PICSO relate primarily to catheter or procedure-related damage, which, in the case of PICSO, is due to prolonged coronary sinus occlusion with insufficient drainage and, in the case of SRP, to inappropriate phasing or an inadequate level of flow and potential hemolysis. Based upon recent information provided by investigators, in several animal preparations, catheters and pump systems for both interventions appear to have proved safe for a period of up to 24 hours. The first human PICSO trials performed during open heart surgery showed no significant catheter-related coronary sinus traumatization (6). For both interventions, adequate anticoagulation is mandatory during the retrograde coronary venous procedure.
Catheter position within the coronary veins has to be checked through angiography to avoid misplacement or damage. Severe traumatization of the coronary sinus may result in rupture and acute tamponade, requiring availability of emergency surgery and shock treatment.

Potential clinical application

Proper patient selection for a new method is clearly crucial for its evaluation and eventual acceptance. Thus, retroinfusion of cardioplegic solutions during open heart surgery appears to be a logical approach for patients with significantly atherosclerotic lesions, which cause severe underperfusion and maldistribution. Nevertheless, controlled trials will still be necessary to prove this technique superior to current methods of cardioplegic delivery.
We presume that either SRP or PICSO will be able to improve ischemia during unstable angina pectoris or salvage myocardium during acute myocardial infarction, and that simple retrograde treatment might also improve perioperative myocardial performance. Probably myocardial protection via the coronary sinus is going to be in use just for a certain period of time, i.e. until even more efficient techniques, such as coronary artery bypass grafting, percutaneous transluminal coronary angioplasty or thrombolysis have been fully established.

Future goals of the Ad Hoc Committee

1. To provide a pool of scientific data on coronary sinus interventions to be judged by the scientific community and government agencies.
2. To collect and share data on a multicenter participatory basis.
3. To promote innovation in order to improve and accelerate the development of useful coronary venous intervention.
4. To develop and critically evaluate clinical protocols aimed at rational applications of the coronary venous intervention.
5. To keep the scientific community informed about the status of technical development and registry through timely and responsible scientific publications.
6. To identify problems which merit further investigation and to motivate those who take a special interest in the field of coronary sinus interventions.

Summary

Recently reported experimental retrograde coronary venous techniques protect the acutely ischemic myocardium and appear to be a sound approach for temporary support of the severely jeopardized myocardium. The current brief report refers to important features of coronary venous interventions, describes apparent improvements, and discusses persisting difficulties in research and developmental evaluation of results. Taking note of the need of informing the scientific community, the recently established International Working Group on Coronary Sinus Interventions (2) wishes to become a forum in which free discussion and criticism should be encouraged in the hope of stimulating research and the development and application of safe methods in the treatment of coronary disease. The eventual objective is to more fully define the limitations of applications and those ranges in which they can be applied without incurring any risks. Our ultimate goal is to maximize the efficiency of applications while at the same time preventing the occurrence of undesirable side effects.

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The so-called "silent zone" of the coronary sinus

M. Tschabitscher

Summary: The coronary sinus and the horizontal section of the great cardiac vein were the subject of an investigation performed in 72 technovit casts, which was to establish the number of posterior left ventricular veins opening into the coronary sinus and the horizontal section of the great cardiac vein and to identify those sections which are not supplied by any such tributaries. A zone with no such venous inflow was found in 58.5% of the preparations tested. In terms of length this zone was found to vary between 20 and 44 mm. This section has been termed "silent zone". Given a coronary sinus length of 20 up to 40 mm, in 40% of all preparations essentially 2 posterior left ventricular veins were found to empty into the coronary sinus. This means that, provided that a silent zone is actually present in a given preparation, this zone is virtually bound to extend onto the horizontal section of the great cardiac vein.
Thus, depending on the longitudinal measurements of the occluding balloon, placement of the balloon may either be such as to occlude one or more venous openings, or may not entrain occlusion, provided that the catheter happens to be placed in any such zone which is not subject to venous inflow (silent zone).

Introduction

The notion "silent zone" is generally associated with that specific section of the coronary sinus in which a balloon catheter may be placed without entraining an occlusion of venous openings. Given due consideration to balloon dimensions, it appears essential, if this term is to be of any use in clinical practice, to assume this zone to be at least 20 mm long. The zone must be located peripherally to the point of entrance of the posterior interventricular vein and, provided that any such vein is present, peripherally to the small cardiac vein. The veins liable to open into this zone have been found to be posterior left ventricular veins. The zone which is not subject to venous openings, hence the zone most suitable for balloon placement, may extend beyond the origin of the coronary sinus, that is beyond the point of entrance of the negligeable left atrial oblique vein of Marshall or the valve of the great cardiac vein of Vieussen respectively, onto the horizontal section of the great cardiac vein.

Material and method

In a total of 72 hearts the coronary sinus and the horizontal section of the great cardiac vein were evaluated as to the incidence of a so-called silent zone. While there was no selection according to age or sex, precise attention was paid to the fact that no obvious pathological-anatomical alterations of the heart were present. To provide for more refined visualization of the veins, the non-fixed hearts were injected with technovit (Kulzer Company). The veins were filled retrogradely from the right atrium.

Anatomical Institute of the University of Vienna (Austria)

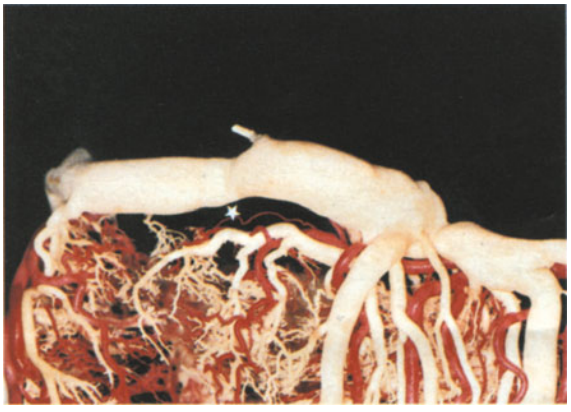

Fig. 1. Technovit cast featuring silent zone which is composed of, in virtually equal parts, the coronary sinus and the horizontal course of the great cardiac vein. Arteries were injected with red contrast medium.
1: point of entrance of the coronary sinus into the right atrium,
2: posterior interventricular vein,
3: coronary sinus,
4: valve of the great cardiac vein of Vieussen,
5: great cardiac vein,
6: posterior left ventricular vein,
7: small cardiac vein,
8: left atrial oblique vein of Marshall,
*: silent zone

Results

A silent zone was found in 58.5% of all material investigated. In only 4.8% of all cases did this zone not extend beyond the coronary sinus. In the remaining 53.7% of all cases the silent zone extended onto the horizontal section of the great cardiac vein (Figs. 1–4). In terms of length the silent zone was found to vary between 20 mm (by definition) and 44 mm, the mean longitudinal extension levelling at 28.8 mm. If we establish a con-

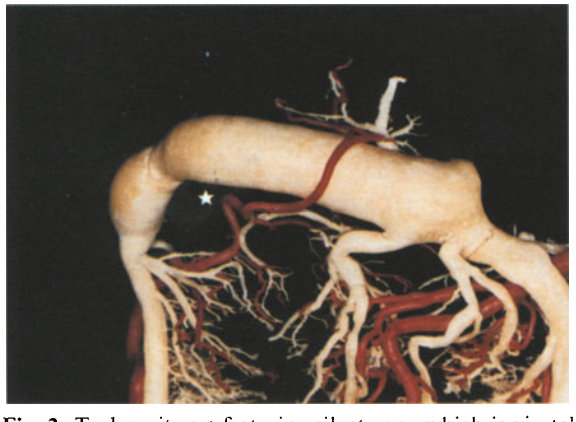

Fig. 2. Technovit cast featuring silent zone which is virutally limited to coronary sinus alone. Arteries were injected with red contrast medium. For key see Fig. 1.

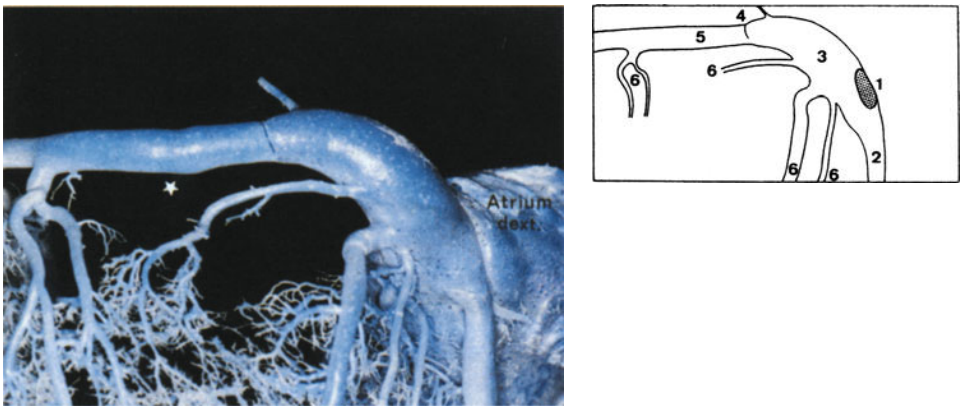

Fig. 3. Overwhelming proportion of the silent zone is located in the great cardiac vein. For key see Fig. 1.

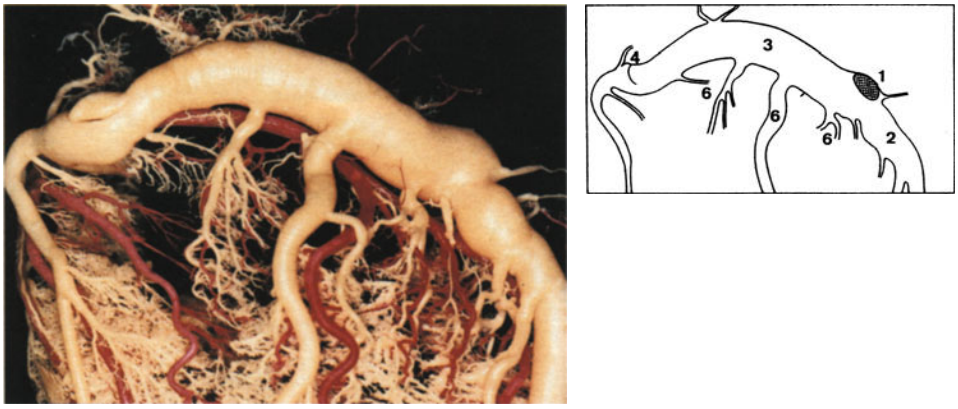

Fig. 4. No silent zone despite unusual longitudinal extension of coronary sinus. Arteries were injected with red contrast medium. For key see Fig. 1.

text between coronary sinus length and the number of posterior left ventricular veins opening into the coronary sinus (Fig. 5), we find that, given a coronary sinus of a length of 20 to 40 mm, it is essentially 2 veins which empty into the coronary sinus. This means that, given a coronary sinus length of any such dimensions, the silent zone, if at all present, is bound to extend onto the great cardiac vein.

Discussion

Ever since the pioneering era of some 40 or 50 years ago with its first fundamental publications (1–3), the coronary sinus has continuously been gaining in clinical importance. This holds true, in particular, with regard to the challenge of coronary sinus catheterization (4, 5). Thus, morphologically speaking, the establishment of parameters such as length, diameter, number of venous openings and the identification of sections which are not subject to venous inflow have gained prevalence; even more so since neither detailed

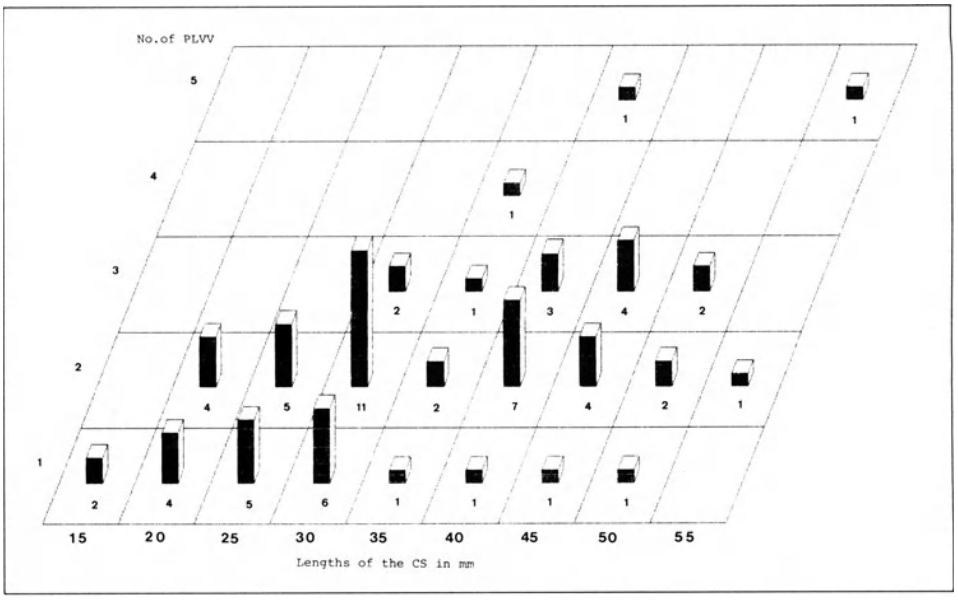

Fig. 5. Variation of number and frequence of posterior left ventricular veins (PLVV) according to coronary sinus (CS) length.

publications (7, 8) nor anatomical text or casebooks (9) have really dedicated themselves to the discussion of any of these parameters.

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Inflow, outflow and pressures in the coronary circulation

T. Kenner, M. Moser, W. Mohl, and N. Tiedt

Summary: The interrelation between arteries and veins and the influence of the myocardial compression during systole is still full of unsolved problems. This study intends to present a rather subjective view of the physical principles which play a role in the perfusion of myocardial blood. These principles are related to the arterial drive, the venous back-pressure which, under certain conditions, may generate a vascular waterfall and a garden hose effect. The vascular waterfall depends on the intramyocardial pressure which increases extra- and intravascular pressure and leads during systole to arterial backward and to venous forward flow. The garden hose effect is due to a distension of vessels by increased transmural pressure. The increase of all pressures in fluid-filled spaces in the myocardium probably has a stabilizing effect on the ventricular shape. An increase of the coronary sinus pressure leads to an increased filtration in the microcirculation. A periodic obstruction and release, interestingly, leads to a net reabsorption of tissue fluid. These fluid shifts can be quantified by the application of continuous blood density recording. The beneficial action of PICSO can be optimized by proper timing of obstruction and release. We assume that PICSO is effective by generation of intramyocardial pressure gradients.

Introduction

The purpose of this study – which does not intend to review the literature – is to discuss some principles of the function of the coronary circulation and, particularly, of the coronary venous system. It is intended to discuss problem areas which are related to the function of pressure controlled intermittent coronary sinus occlusion (PICSO). It seems important to note that, more pronouncedly than in any other organ, the coronary veins are functionally influenced by and dependent on the arterial inflow and the surrounding myocardial tissue of the local vascular bed. Pressures and flows in the veins are determined by the driving pressure, the pressure gradient between intravascular space and tissue and some special hydrodynamic phenomena at the sites of the venous outflow where the blood enters the atria or the ventricles. Furthermore, we will discuss the function, application and validity of a new method which we use to observe variations of flow, filtration and reabsorption of fluid in the myocardial microcirculation.

Some remarks on morphology

Similar to the large coronary arteries which are situated on the epicardial surface and give off branches perpendicularly into the myocardium, the most important of the large venous channels run on the epicardial surface and converge into the coronary sinus, as shown in Fig. 1.

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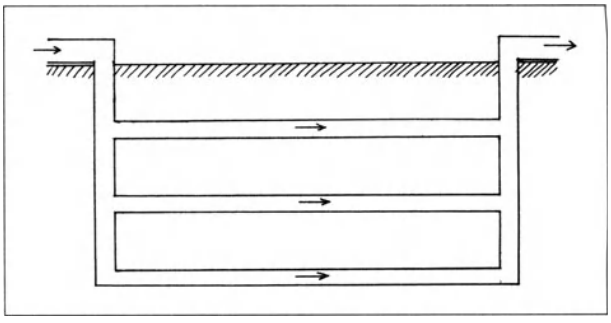

Fig. 1. Schematic drawing showing the distribution of inflow and outflow vessels in the myocardium.

Besides these epicardial veins, the so-called anterior superficial veins drain mainly the right ventricle and empty separately into the right atrium. The so-called Thebesian veins enter directly into all four chambers of the heart (14, 22).

Although the coronary sinus leads the main fraction of the myocardial venous blood, a complete occlusion of the sinus reduces the left main coronary inflow in the dog by only 8% (13). This can be explained by the presence of quite prominent interconnections between the large coronary veins. – Even the complete occlusion of coronary sinus and anterior veins can be survived for at least several hours (13). Thus, even under this extreme condition there are still enough functional collaterals to provide sufficient outflow from the coronary vascular system.

It may be helpful to discuss the influence of the venous shunt resistance R_{sh} with the help of a very simple model shown in Fig. 2. p_A is the arterial driving pressure. R_c is the coronary microvascular resistance. P_{cs} is the coronary sinus pressure which is increased by the partial or complete occlusion of the coronary sinus. The corresponding variable resistance is shown as R_{cs}.

A simple calculation shows that

$$p_A = q_c R_c \tag{1}$$

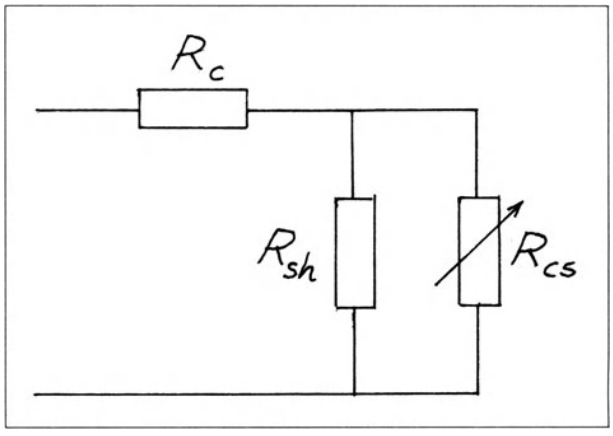

Fig. 2. Distribution of flow resistances in the myocardium R_c coronary microcirculatory resistance R_{sh} venous shunt resistance R_{cs} resistance of a coronary sinus obstruction.

as long as the coronary sinus resistance is negligible as under normal conditions. The effect of complete occlusion is described by:

$$p_A = q_c(R_c + R_{sh}) \tag{2}$$

Therefore, as is obvious, all hemodynamic variations after coronary sinus occlusion depend on the magnitude of the shunt resistance.

Determinants of coronary flow

We have in earlier studies described a simple model in terms of a windkessel equation for the coronary arterial inflow q_c (4, 5):

$$q_c(t) = \frac{p_A(t)-p_{cs}(t)}{R(t)} + \frac{dp_A}{dt} C_c \tag{3}$$

$q_c(t)$ coronary arterial inflow
$P_A(t)$ aortic pressure
$R(t)$ time dependent coronary resistance
C_c coronary arterial compliance
The time dependent coronary resistance can be estimated as:

$$R(t) = \frac{R_c}{1-Hp_v(t)/p_A(t)} \tag{4}$$

where
R_c constant fundamental value of the coronary resistance.
H weighting function (dimensionless, between 0 and 1) describing the myocardial squeezing of the intramural vessels.
$P_v(t)$ left ventricular pressure
R_c corresponds to the diastolic resistance value of the coronary vascular bed which is reached if either the ventricular pressure is zero or if H = O, a condition which usually can never occur, not even in noncontractile left ventricular wall. In the right ventricle H is rather small and may be neglected without much error.
This equation indicates in a concise form the most important magnitudes and their functions, which determine the flow into the coronary system.
The effect of the coronary sinus pressure p_{cs} has been assumed simply to be additive: the larger p_{cs} the smaller the "driving pressure head" in the first term of Eq. (3). In other words, if the coronary sinus pressure is increased by Δp_{cs} then the pressure head on the arterial input side is decreased by this amount.
The squeezing effect is assumend here in first approximation mainly to act on the resistance vessels. H in Eq. (4) is nearly zero in the right ventricle and about 0.7 to 0.8 in the left ventricle (5, 6).
The second differential term in the windkessel equation is able to explain a pulsatile flow peak due to a steep aortic pressure pulse, and a negative value of the coronary arterial inflow during the fast decline in the aorta. As will be discussed below, there is, however, another more important reason for a negative systolic peak in the coronary arterial flow.

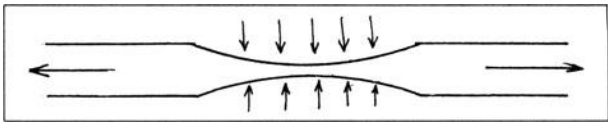

Fig. 3. Schematic drawing indicating the forward and backward flows produced by myocardial squeezing.

Myocardial squeezing

As described by Tiedt (21) and discussed recently by Hoffman et al. (2) the systolic myocardial pressure rise squeezes the intramural arteries, capillaries and veins. Independent of the question of intramyocardial pressure distribution this squeezing leads as an overall effect to a marked systolic arterial backflow and simultaneously to an increased venous forward flow. In the coronary arteries negative flow or "backflow" is added to the flow which can be calculated from Eq. (3). A corresponding term (q_{sqa} squeezed flow into the arteries) can be written

$$q_{sqa} = -\alpha dV/dt \tag{5}$$

where α is the fraction of vascular space squeezed backwards into the arteries.
V is the compressed vascular space as shown in Fig. 3.
The corresponding venous forward flow q_{sqv} equals

$$q_{sqv} = (1 - \alpha)\, dV/dt \tag{6}$$

It is interesting to mention here that in many articles – even in handbooks – this fundamental connection between microcirculation, arteries and veins is neglected completely. Often the description starts very detailed with the arteries, proceeds somewhat less completely with the capillaries, and leaves out the veins.

Arterial zero flow intercept

As described by Ronniger (18) and by Wetterer and Kenner (24) the phenomenon of zero flow intercept is due to the nonlinearity of the pressure flow relation in the resistance vessels. This interpretation has been well proven for several arterial beds and for the arterial system as a whole (24).
There is no reason to assume that the behaviour of the myocardial vascular system should be any different. The possible influence of a vascular waterfall phenomenon is not necessary for the fundamental interpretation of the zero flow intercept. However, this phenomenon may play a role in that it increases the pressure in the intramural veins and thus may shift the zero flow pressure value (23).
In terms of Eq. (3) the zero flow intercept at pressure p_{zf} can be described by subtracting this pressure term from the aortic pressure. The resistance R_c then has to be interpreted as the differential value of the resistance. Furthermore, we have to consider that under this more complex model assumption the influence of increased intramural venous pressure takes the lead in shifting the zero flow pressure value as soon as it increases above p_{zf}. The latter is the zero flow intercept determined in relaxed myocardium.

In the coronary vascular system therefore, several mechanisms are in functional interaction: a) the nonlinearity of the peripheral resistance R_c; b) the effect of squeezing by the myocardial contraction on the resistance R(t); c) the effect of squeezing on arterial and venous vascular spaces leads to a combined outflow from these vessels backward as well as forward; d) the effects from the venous side mainly depend on the magnitude of the venous pressure; and e) a vascular waterfall phenomenon may increase the actual zero flow pressure value.

Pressure distribution in the myocardium

The problem of pressure distribution in the myocardium and its effects on flow is still an unsolved problem of measurement technique, although many attempts have been published. There are differences in opinion about the height of the pressure values and about the question if intramyocardial pressure can be higher than the ventricular pressure.
Basic agreement is found on the existence of an endocardial-epicardial pressure gradient. Most measurement techniques indicate that the myocardial pressure during contraction equals the ventricular pressure at the endocardial surface and declines to zero towards the epicardial surface.
Here three aspects will be discussed. First, Noordergraaf's group (17) recently presented a simple theoretical calculation the results of which look surprising at the first sight. In several earlier studies the intramyocardial pressure p_{im} was simply equated with wall stress in the radial direction. Noordergraaf assumes that p_{im} can be interpreted as the pressure in a minute fluid pocket in the myocardium. Then its value equals the average of the three perpendicular wall stresses acting upon it. For a thick walled cylinder as well as for a sphere p_{im} turns out to be independent of the location in the wall. For the cylindrical thick walled tube:

$$p_{im} = \frac{r_i^2}{r_e^2 - r_i^2} \quad p_v \tag{7}$$

where
p_v ventricular pressure
r_i inner radius of the cylinder
r_e external radius of the cylinder
Thus, p_{im} is critically dependent on geometric conditions – as will be discussed below – and may indeed exceed the model's chamber pressure (17).
Secondly, in a study on the forces in the arterial wall (7) the possibility was pointed out that in a cylindrical vessel with circumferential muscles in the wall the pressure distribution in the wall has to depend on the radial distribution of muscle activation. If only the inner muscle layer is activated, the intramural pressure is high in the innermost layers. If only the outermost layer of the vascular cylinder is activated, the pressure in all layers and wall tissues would be increased.
Thirdly, as Lunkenheimer et al. (12) have shown and discussed, the myocardium is not a homogeneous cylinder, but is composed of fibers which may have quite complex configurations and topographic features. – As a consequence the pressure distribution within the myocardium depends on geometric, structural and regulatory conditions.

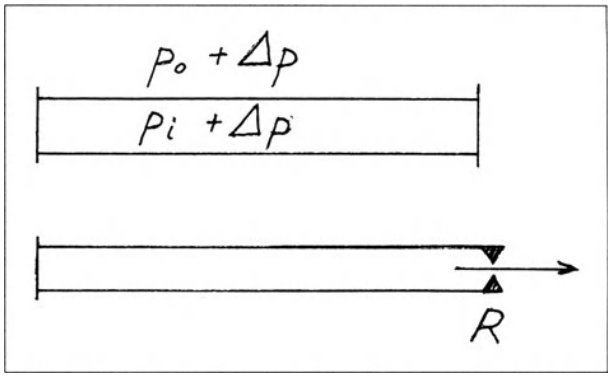

Fig. 4. The pressure in a fluid-filled collapsible tube increases by the same amount Δp as the squeezing pressure. If fluid leaves through a resistance, R, the vessel will collapse only after complete emptying.

Distribution of systolic and diastolic squeezing

The foregoing paragraph shows that the problem of intramural pressure distribution in the ventricular walls is still unsolved. There are two further important facts. Spaan (20), Hoffman (2) and other authors have pointed out that, whenever the intramyocardial pressure increases during systole, the squeezed vessels not only and simply collapse, but first the pressure in the vessels will also increase. Since the generation of flow depends on the presence of a pressure gradient, the latter is the more interesting and important magnitude which should be discussed here.

Quantitatively, as shown in Fig. 4, the pressure increase inside a vessel equals the pressure increase outside the vessel, the latter being the source of the compression. This condition holds exactly as long as the vessel is not allowed to empty. If this vessel is allowed to empty through a resistance R into another vascular area (collateral artery or vein) inside which the pressure is somewhat lower, the intravascular pressure will stay at the high level until collapse occurs. This process, symbolized in Fig. 4, is not only important for the intramycardial hemodynamics but also for the dynamics of cardiac contraction, as discussed shortly in the next paragraph.

Intramyocardial hydraulics

The term intramyocardial hydraulics was introduced by Lunkenheimer et al. (12) to describe the assumption that the coronary blood and all liquid mural components in the ventricular wall have the function of what the authors call a hydraulic fulcrum. In part, therefore, the ventricular wall can be assumed to function like an erectile tissue. One part of the wall properties originates from the vascular spaces as discussed above, another part has something to do with intramyocardial fluid spaces between muscle fibers. Lunkenheimer et al. (12) assume as third component of the wall properties, the spatial force component of a threedimensional myocardial network, which suggests a transmural force vector which opposes the systolic increase in wall thickness. Whatever the components of the ventricular wall properties may be, all these components act upon the deformable but incompressible "fulcrum" of intramyocardial fluid spaces and thus help the heart to stabilize its shape during contraction. This effect actually means a generalization of the purely vascular garden hose effect to the whole myocardium (see below).

Lymph flow

All the above considerations can also be applied to the myocardial lymph vessels and to myocardial lymph flow.
In each myocardial layer an increase in intramyocardial tissue pressure will also increase the pressure in lymphatic vessels. With the exception of location where the myocardial contraction generates marked pressure gradients along a lymphatic vessel, there will be no change in lymph flow due to the increase of the intramural pressure, as compared to the condition during myocardial relaxation.

Local failure of contraction as cause of fluid displacement

A local failure of contraction in the myocardium of the ventricular wall leads to local bulging and therefore to an increase of the corresponding local ventricular radii.
If we assume a simple cylindrical model of the ventricle, the condition of constant volume during contraction or relaxation can be written as

$$r_a^2 - r_i^2 = \text{const} \tag{8}$$

Insertion of this equation into Eq. (7) yields the information that in this model the intramyocardial pressure

$$p_{im} = r_i^2 \, p_v/\text{const} \tag{9}$$

depends on the inner (and/or of course, according to Eq. (8) on the outer) radius of the ventricular cylinder and on the ventricular pressure. – We can assume from this simple calculation, that under the given condition the intramural pressure will be higher in the distended area than in the area which contracts normally.
It is important and interesting, that there is no difference between wall stress and intramural pressure in an actively contracting and in a passively distended area of a ventricular cylinder. The forces and pressures only depend on the dimensions and on the ventricular pressure according to Eq. (7) or (9).
Along the pressure gradient between a more distended myocardium (higher intramural pressure) and a normally contracted myocardium fluid can be displaced. This conclusion applies as well for blood as for other fluids.
It may be argued that the condition of homogeneity assumed in Noordergraaf's model does not apply in reality and that all actual recordings of intramyocardial pressures reported in the literature observed a radial pressure gradient in contrast to this model. However, one may answer that on the one hand the problem of measurement technique is still unsettled, while on the other hand even under somewhat differing conditions a pressure gradient has to exist between a more distended and a neighbouring normal segment. So the basic consequence seems to be independent of the particular model.

Outflow from the coronary sinus

In all the locations where cardiac veins empty into a ventricular or into an atrial chamber, the vein suddenly opens into a large space. This is also true for the coronary sinus. In such a location the following relation between pressure and flow can be found (16):

$$p_{ven} - p_{atr} = \rho_B v^2/2 \tag{10}$$

The terms on the left side correspond to the pressure gradient between vein and atrium. v is the flow velocity and ρ_B the density of blood. Related to the volume flow in the vein q the equation can be written in the following form, where $A = r^2\pi$ is the cross sectional area of the orifice:

$$p_{ven} - p_{atr} = \rho_B q^2/2A^2 \tag{11}$$

For average flow values in the coronary sinus of around 3 ml/s the pressure gradient at the orifice is immeasurably small. It may increase to about 1 to 2 mm Hg if peak values of pulsatile outflow of 30 to 50 ml/s occur. Of course the pressure gradient may increase in the case of a stenosis at the orifice. Also the reduction of the free orifice by the presence of a catheter may increase pressure gradients.
In any case it seems important to note that pressure gradients at such an orifice are proportional to the square of the flow velocity.

Some remarks on the "waterfall phenomenon"

The condition for the occurrence of a so-called waterfall phenomenon is a vessel or a system of vessels which leads through areas in which local differences of the outside pressure exist. The usual simple model is shown in Fig. 5, where a collapsible tube leads through a chamber in which a pressure exists which is higher than the pressure at the entrance or outlet of the tube.
This condition is certainly given in the coronary vascular system (23), particularly if we consider the contracted state of the myocardium in systole. This intramural part of the coronary circulation corresponds to the collapsible tube within the chamber shown schematically in Fig. 5. If fluid flows through such a system, a natural collapse occurs where the vessels leave the higher pressure surrounding. This is what we call the waterfall phenomenon. The question of whether this phenomenon influences the relation between input pressure and flow has been discussed above. In our opinion, the critical closing pressure due to the nonlinearity of the pressure flow relation can be interpreted without this phenomenon. On the other hand an effect on the venous pressure cannot be denied.
Collapsible tubes show under certain conditions very remarkable properties, which, for example, produce properties of a valve (6). As discussed in the cited paper two stable flow conditions seem to be possible which depend on the time history of the collapsible

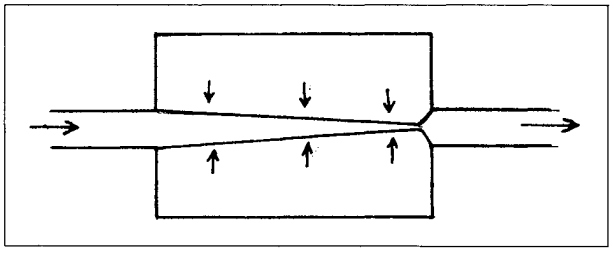

Fig. 5. Scheme of a collapsible elastic tube in a compression chamber. A so-called waterfall phenomenon appears at the outflow side of the chamber if the pressure in the chamber is higher than the downstream pressure p_{vq}.

system – i.e. whether a certain condition is reached during increasing or decreasing flow values. These conditions may have to be considered when questions of optimality of flow and transport conditions are discussed (see below).
We think however, that the periodic collapse of all intramural vessels during systole is the more important phenomenon (21), because this periodic collapse leads to a forward or backward flow of the expelled fluid. – The study of non stationary flow and pressure in collapsible tubes is still quite an open field of research.

The garden hose effect

Any increase of transmural pressure in a cylindrical fluid filled space leads to the generation of distending wall stresses in all directions. This effect is called the garden hose effect (13). In the case of a thin walled vessel with wall thickness h the longitudinal stress is

$$\sigma_l = p\, r / 2\, h \tag{12}$$

The circumferential stress in a non tethered vessel has twice this value:

$$\sigma_c = p\, r / h \tag{13}$$

The corresponding force in longitudinal direction is

$$F_l = r^2\, \pi\, p \tag{14}$$

The circumferential force depends on the length of the vessel segment l:

$$F_c = r\, l p \tag{15}$$

In all equations p is the transmural pressure difference (7). The forces given by Eqs. (14) and (15) distend the tissue surrounding a filled vessel. F_l can be interpreted as being equal to that compressing force which a pillar with the radius r can carry before collapsing. It is obvious that the total force of several parallel vessels depends on the total cross sectional area of the vessels. The crucial variable however is the transmural pressure p. Therefore, it seems that the overall effect of distension in veins and capillaries is negligible as long as normal pressures prevail. During an obstruction of the venous outflow a garden hose effect may be present, particularly during diastole.
It has been mentioned above that basically the same garden hose or "distension" effect is induced by the muscular contraction of the ventricles themselves. During their contraction, all fluid spaces in the myocardium – including the vascular spaces – are pressurized by the squeezing force and therefore, as Lunkenheimer et al. (12) state, act as fulcrum for the myocardial contraction.

PICSO

In order to describe the mechanism of PICSO in a somewhat simplified manner, in an earlier publication we introduced the term "turbo charger effect" (6). This term is sup-

posed to indicate that an increase of the outflow pressure leads to an improvement of the system's performance.
What actual effect has an increase of the venous outflow pressure by obstruction of the coronary sinus? There are at least two immediate effects:
a) The blood content of the veins is transiently increased and b) therefore, the coronary veins are distended by blood, thus producing a garden hose effect. As a consequence, vascular areas which are underperfused from the obstructed arterial side are filled from the venous side. Since the contractility of the corresponding site of the ventricular wall is reduced, this site is more distended than its normal neighbourhood. This, in turn, leads to a systolic increase of the intramural pressure – as discussed in an earlier paragraph – and thus permits an overall increase of washout effects. One component of washout corresponds to an increased transfer of tissue fluid from the lesioned area into the blood. This effect, which can be interpreted as reduction of edema in or around an underperfused area, was studied by the application of a method for the continuous recording of blood density (8). The method will be briefly discussed in the following paragraph. We were able to observe that PICSO leads to a reduction of the arteriovenous density gradient, which indicates that the venous blood is diluted by fluid entering the blood in the microcirculation from the tissue space. The dilution of the venous blood by fluid entering the blood is schematically shown in Fig. 6.
The improved overall washout has also been proven by Chiuffo et al. (1).

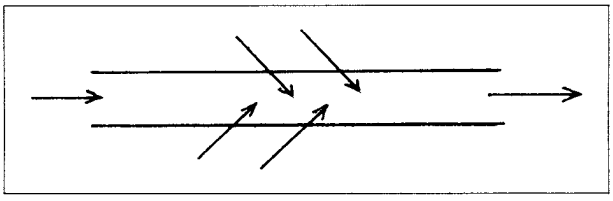

Fig. 6. If extravascular fluid enters a vessel (arrows) through an absorption process then the blood density at the venous outflow decreases (and vice versa).

The measurement of blood and plasma density

The continuous measurement of blood density has been performed with the so-called mechanical oscillator method which was developed by Kratky et al. (11) and was first introduced for the recording of capillary fluid exchange by Kenner et al. (9). The method is based on the measurement of the oscillation frequency of a small glass oscillator which is continuously perfused with blood (10). Plasma density can be measured with the same method from samples of blood after centrifugation.
The oscillation frequency of the fluid filled glass oscillator depends on the elasticity of the oscillator and on the density of the perfused fluid. The accuracy of the method is better than 0.01 g/l. It has been proven that viscosity of the fluid has no influence on the recording (8). The density of the blood ρ_B depends on the hematocrit H and on the density of erythrocytes ρ_E and of plasma ρ_P:

$$\rho_B = \rho_E H + \rho_P (1-H) \tag{16}$$

Loss of fluid from the blood in the microcirculation by filtration leads, as shown experimentally, to an increase of the density of venous blood and of venous plasma (8) in the

order of magnitude of 0.1 g/l. During PICSO we have observed a reversal of this gradient. This indicates that during this procedure more fluid is reabsorbed from the tissue into the blood. This has been discussed in the previous paragraph.
The method used in our study is one of the possible methods which can be applied to observe changes in washout from underperfused areas. This particular method has the advantage that simultaneously or intermittently with the recording of spontaneous arteriovenous density differences, flows and volumes can also be measured with the application of density dilution methods. These procedures are analogous to all dilution methods, except that the injected indicator must have a density which differs from blood density and thus can be recorded by the same continuous density recording as described above.

The problem of optimization of PICSO

The effect of an obstruction of the coronary sinus is two-fold. A permanent obstruction and increase of the venous pressure leads to an increase of capillary filtration and lymph production (8). This effect can be observed by continuous recording of the arteriovenous density difference. A brief obstruction of the coronary sinus leads to a transient reduction of the density gradient which is particularly related to the time of reopening of the coronary sinus. We interpret this decrease as being the functional indication of the washout effect of PICSO. A periodic obstruction and reopening of the coronary sinus, thus permits the summation of the washout effects. A precondition of a most beneficial effect is a proper optimal timing. We have already made some observations on a) a method for testing optimal time intervals and b) found that obstruction periods of 9 to 10 s followed by release intervals of 8 s seem to provide the best results (15).
The fact that a summation of washout effects is possible can be explained by the asymmetry of the filtration and reabsorption process induced by transient coronary sinus occlusion.

Reflexes and regulatory mechanisms

Distension of the coronary veins not only leads to the hydrodynamic changes described in the earlier paragraphs, but induces bradycardia and blood pressure reduction through a mechanoreceptor reflex (4). Such a mechanism permits the left ventricle to reduce its energy output, and thus may contribute to saving myocardial tissue during ischemia. This reflex can be elicited by an increase of the coronary sinus pressure.
It has been observed, furthermore, that a reduction of coronary flow by less than 50% leads to a decrease in contractility and therefore tends to reduce the energy consumption of the myocardium (3, 19). The arteriovenous difference of the oxygen concentration surprisingly does not rise but in fact decreases during this process. It seems that the myocardium reacts to a decrease in oxygen delivery rather like a primitive cell, the energy consumption of which is purely dependent on input and output without an attempt of a homeostatic control mechanism. Since an increase of the coronary sinus pressure reduces coronary blood flow, the resulting reduction of energy turnover may contribute to the beneficial effect of PICSO.

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Coronary sinus interventions: clinical application

A. K. Jacobs

Summary: Over the past decade there has emerged a renewed interest in the coronary sinus as a means of treating acutely jeopardized myocardium. Numerous studies from multiple investigators support the fact that the coronary sinus interventions will play a role in the treatment of several ischemic syndromes. There is strong evidence to suggest that SRP and PICSO will be effective in salvaging myocardium during myocardial infarction as well as during reperfusion. Retroinfusion via the coronary sinus of cardioplegic solutions or pharmacologic agents appears to be a promising technique in selected patients. Current clinical studies will probably document a role for PICSO in the reperfusion period during cardiac surgery.

As with any new therapy, the coronary sinus interventions will of necessity be as good as or better than current medical and or surgical therapy. Towards this end, the coronary sinus techniques will require evaluation against standard therapy or in combination with accepted treatments. In addition, the advantages and disadvantage of each technique must be weighed individually and compared to each other. As a group, the coronary sinus techniques offer a method of myocardial protection which provides access to an ischemic microvasculature. Coronary sinus catheterization is relatively simple to accomplish both in open as well as close-chest subjects. The major disadvantage is the potential for damage to the venous system.

Specifically, the advantages of retroinfusion of cardioplegic solutions are 1) avoidance of trauma to the coronary arteries especially in patients with ostial left main coronary disease, 2) minimal interference with the surgical procedure in 3) more uniform distribution of cardioplegia in patients with proximal coronary artery stenoses. Major disadvantages include 1) potential for inadequate protection of the right ventricle, 2) longer time to diastolic arrest, 3) potential for coronary venous injury and 4) an extra right atrial incision. The advantages of SRP include 1) retroperfusion during diastole with normal venous flow during systole and 2) potential to deliver pharmacologic agents to an ischemic microcirculation. Disadvantages include 1) need for arterial access and 2) potential for hemolysis. The advantages of PICSO are similar to those of SRP in addition to the fact that PICSO is a simple system without the need for arterial access. PICSO also probably facilitates washout of edema and ischemic metabolites and there is the potential for hemodynamic monitoring. The major disadvantage of PICSO is that it may not be effective for acute myocardial ischemia, i.e. in acute coronary insufficiency.

Of utmost importance is that any new method must be shown to be safe. Preliminary experimental and clinical studies have been encouraging in that there has been no evidence of major vascular damage due to the application of the coronary sinus techniques. Coronary sinus pressure should be monitored to avoid excessive pressure, prolonged coronary sinus occlusion and inappropriate cycling. Currently, safety considerations in catheter design and pump systems are being investigated.

Introduction

The effective treatment of the functional consequences of acute myocardial ischemia and, more specifically, the reduction in infarct size, morbidity and mortality is a major research goal in the field of cardiology today. Extensive studies of pharmacologic interventions, thrombolytic therapy with intracoronary and intravenous streptokinase and more recently with tissue plasminogen activator and intraaortic balloon circulatory assistance continue to search for an acceptable mode of treatment of acute ischemia.

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The concept of perfusing ischemic myocardium retrogradely via the coronary veins which are generally free of atherosclerotic involvement is not new. Retrograde perfusion and arterialization of coronary veins were conceptualized by Pratt in 1898 (33), later studied by Wearn (38) and then applied by Beck (3) in the early 1940s prior to the introduction of the present day coronary artery revascularization surgery. The Beck procedure involved shunting of blood from the aorta into the coronary sinus which was subsequently constricted to elevate pressure in the coronary vein and thus ensure delivery of arterial blood into ischemic zones of the left ventricle. Early experimental data and clinical application appeared promising; however, the operation was associated with excessive mortality. There was some evidence that prolonged stenosis of the coronary sinus, with elevated venous pressure, was associated with vascular as well as myocardial damage.
Over the past several years there has been a revival in the concept of using the coronary sinus to gain access to ischemic myocardium. Extensive experimental as well as clinical studies are now documenting a role for coronary sinus instrumentation in the treatment of acute ischemic syndromes. Specifically, coronary sinus interventions have been evaluated in the setting of evolving myocardial infarction, myocardial infarction in the presence of reperfusion and during brief myocardial ischemia. In the surgical arena, retroinfusion via the coronary sinus of various cardioplegic solutions and intermittent coronary sinus occlusion during coronary bypass surgery are currently under investigation. In addition, measurement of coronary sinus pressure in critically ill patients has important diagnostic potential.

The coronary sinus techniques under clinical consideration include:

1) Retroinfusion of cardioplegic solutions

This technique has undergone extensive clinical and laboratory investigation. Initial studies, detailed below, appear promising and suggest that retroinfusion of cardioplegia would be an excellent alternative in selected patients.

2) Retroperfusion

a) Selective arterialization of coronary veins has been shown to reduce experimental infarct size (30) and distribute arterial blood throughout all layers of the myocardium [14].
b) Synchronized retroperfusion (SRP), that is retroperfusion of arterial blood synchronized to diastole, allowing normal venous flow in systole, has enjoyed a decade of detailed evaluation. Experimental studies have clearly shown that this technique, when performed during coronary artery occlusion, improves myocardial metabolism and left ventricular function (24), favorably redistributes blood flow toward the endocardium (4) and results in reduction of the ischemic zone and ultimate infarct size (8).

3) Pressure controlled intermittent coronary sinus occlusion (PICSO)

Intermittent occlusion of the coronary sinus, without arterialization or synchronization to diastole, is performed while coronary sinus pressure is monitored continuously. To allow sufficient filling of the central ischemic area as well as adequate venous drainage the oc-

clusion versus release phase of the cycle is controlled by the coronary sinus occlusion pressure. That is, the coronary sinus is occluded until the elevated systolic sinus pressure reaches a plateau; coronary sinus obstruction is then released facilitating venous drainage and a return to baseline pressure. The cycle is repeated and the timing adjusted as dictated by the coronary sinus pressure. This technique has also been shown to reduce experimental infarct size (28) and improve ischemic zone left ventricular function (29) during myocardial infarction as well as in the setting of infarction and reperfusion (18).

Clinical indications

1) Acute myocardial infarction

Numerous experimental studies have provided persuasive evidence that both SRP and PICSO may have a clinical role in the treatment of an acute myocardial infarction. In the early 1970s Meerbaum and Corday (24) developed the procedure now known as SRP. This technique differs from the Beck procedure and other surgical techniques. First, synchronization provides retroperfusion of arterial blood during diastole, allowing normal physiologic coronary venous drainage during systole. Second, the method is intended as a temporary treatment for acute myocardial ischemia while awaiting definitive therapy. The effectiveness of coronary venous retroperfusion treatment of an ischemic myocardial segment was assessed by measurements of regional and global myocardial function in 16 dogs. The left anterior descending artery was acutely occluded for 75 minutes. After 30 minutes of occlusion, SRP was instituted for 45 minutes by synchronized pumping of arterial blood from the brachial artery into the anterior interventricular coronary vein.

Retroperfusion resulted in significant improvement from the level of regional dysfunction observed after 30 minutes of occlusion: ischemic zone myocardial force increased 106 percent, epicardial S-T elevation decreased 46 percent, normalized peripheral left anterior descending coronary arterial flow increased 50 percent and distal left anterior descending PO_2 decreased 44 percent. These regional improvements were significant when compared with findings in an untreated series of 12 dogs with 75 minutes occlusion of the left anterior descending coronary artery.

Diastolic-augmented coronary venous retroperfusion with arterial blood provided significant but not complete restoration of function in the ischemic segment. Therefore, the authors reasoned that this technique may represent a useful temporary support to an otherwise inaccessible jeopardized region of the myocardium. This provocative study was subsequently corroborated by Farcot et al. (8) who demonstrated that in a similar canine model, SRP significantly reduced infarct size and improved ischemic zone dysfunction. In 1981, Smith and colleagues (35) reproduced these results in baboons using early retroperfusion combined with late arterial reperfusion. In 1982 Meerbaum et al. (23) reported that hypothermic SRP protects reversibly injured ischemic myocardium and improves cardiac function. Most recently, Drury and colleagues (7) reported the results of a preclinical safety and efficacy study using a new synchronized diastolic retroperfusion mechanical pump and autoinflatable balloon catheter. In dogs, SRP starting 30 minutes following occlusion of the left anterior descending artery and continuing until sacrifice at 6 hours significantly reduced infarct size (19 ± 18 vs. 58 ± 36 percent of the area at risk)

as compared with 8 control dogs. Morphologic examination of the coronary sinus and cardiac veins did not demonstrate evidence of damage due to SRP. There was also no evidence of excess myocardial edema in either the jeopardized ischemic or normally perfused zones. Significant red cell hemolysis or platelet destruction did not occur. Therefore, the authors concluded that SRP is a safe and effective treatment of acute myocardial infarction in experimental animals and warrants clinical testing.

In the early 1980s Mohl first described the technique of pressure controlled intermittent coronary sinus occlusion (PICSO). With his colleagues he reported the effects of PICSO during experimental myocardial infarction (28). PICSO was performed by means of a pump system which produced controlled, intermittent occlusion of the coronary sinus and used coronary sinus pressure as a feedback to determine the duration of occlusion. PICSO begun 15 minutes after occlusion of the left anterior descending artery in 13 dogs and continued for 6 hours resulted in 45 percent reduction in infarct size (56 percent of risk region) as compared to 12 untreated dogs (99 percent of risk region) as shown in Fig. 1. Mohl concluded that PICSO salvages ischemic myocardium and may provide an effective treatment during acute myocardial infarction. These results were corroborated by Ciuffo and colleagues (5) in a model of 3 hour coronary artery occlusion. PICSO starting 30 minutes following the onset of ischemia reduced infarct size from 56.7 ± 8.1 to 15.1 ± 5.9 percent of the myocardium at risk.

Therefore, review of the existing data strongly supports a role for both SRP and PICSO in the treatment of acute myocardial infarction. Experimental studies document significant salvage of jeopardized myocardium and suggest the need for clinical evaluation.

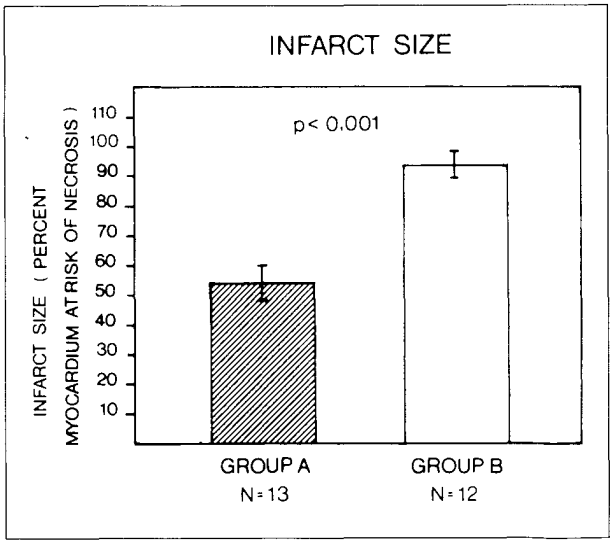

Fig. 1. Effect of PICSO on infarct size expressed as percent of myocardium at risk. Mean ± SE. Group A: dogs treated with PICSO. Group B: untreated controls. From: Glogar et al. (1984) Pressure controlled intermittent coronary sinus occlusion affects the myocardium at risk and reduces infarct size. In: Mohl W, Wolner E, Glogar D (eds) The Coronary Sinus. Steinkopff Verlag, Darmstadt, p 450

2) Acute myocardial infarction in the setting of reperfusion

With the advent of clinical reperfusion techniques such as percutaneous transluminal angioplasty and thrombolysis, evaluation of the coronary sinus techniques in the setting of reperfusion seems warranted. The studies by Meerbaum and colleagues suggest that cor-

onary sinus interventions provide only temporary support of jeopardized myocardium (39). It has yet to be determined whether SRP or PICSO, when combined with definitive revascularization, will enhance myocardial salvage.

To test the hypothesis that PICSO performed in the presence of reperfusion reduces infarct size more than reperfusion alone, Jacobs and colleagues (17) studied 28 open-chest anesthetized dogs. Proximal occlusion of the left anterior descending artery for 3 hours was followed by 3 hours of reperfusion. Dogs were randomly assigned to PICSO plus reperfusion or reperfusion alone 30 minutes following left anterior descending artery occlusion. PICSO was performed using a pump inflated coronary sinus balloon-tipped catheter until the coronary sinus occlusion pressure reached a plateau (10 seconds). The balloon was then rapidly deflated (4 seconds) and the cycle repeated throughout occlusion and reperfusion. Risk region was determined by Rhodamine B perfusion and infarct size was measured using triphenyltetrazolium chloride staining.

Analysis of the data revealed that both groups of dogs (reperfusion alone, n = 11; reperfusion plus PICSO, n = 11) were comparable in that left ventricular mass, grams of risk region and percent of the left ventricle at risk of infarction were all similar. However, the addition of PICSO resu[redacted]n a significant decrease in infarct size from 10.3 g (reperfusion alone) to 4.8 g (rep[redacted]on plus PICSO) of total infarct size.

As shown in Fig. 2, in [redacted]perfusion group, 33 percent of the myocardium at risk was infarcted. PICSO beginning 30 minutes after coronary occlusion and continuing throughout 3 hours of reperfusion resulted in an additional significant decrease in infarct size, with only 16 percent of the region at risk infarcted. Therefore, although reperfusion alone salvaged over 60 percent of the risk region in this model, PICSO significantly enhanced salvage with 85 percent of the area at risk of infarction ultimately spared from myocardial cell necrosis.

The authors concluded that in this experimental canine model, PICSO administered early after coronary artery occlusion significantly enhances the salvage of ischemic myocardium achieved by reperfusion alone.

These data suggest that intermittent obstruction of the coronary sinus, performed during evolving myocardial infarction, may have a role in the clinical setting of acute myocar-

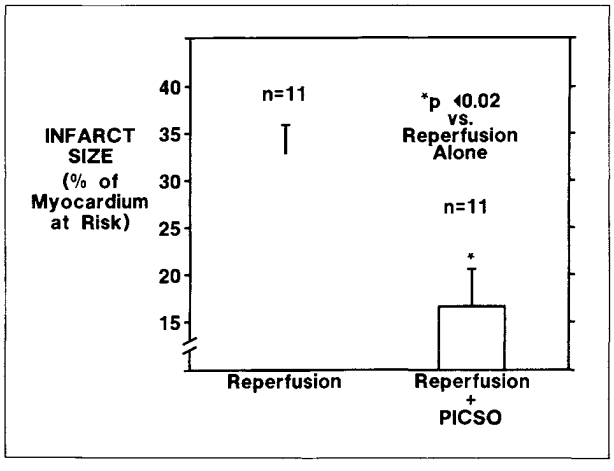

Fig. 2. Effect of PICSO during reperfusion on infarct size expressed as percent of myocardium at risk. Mean ± SE

dial infarction and reperfusion by coronary angioplasty and/or thrombolysis. However, although it is now well accepted that arterial reperfusion, if performed early enough, salvages ischemic myocardium, it has been shown that this reperfusion is also associated with additional cellular damage and early cell swelling (6). Hence the concept of "reperfusion injury" has emerged. Preliminary studies by Mohl et al. (26) have suggested that PICSO enhances washout of myocardial edema and toxic metabolites accumulated during ischemia. Therefore, the coronary sinus techniques, by altering pressure-flow relationships in the venous system, may reduce cell swelling and potentiate the salvage of ischemic myocardium achieved by reperfusion. To test the hypothesis that SRP or PICSO reduce reperfusion injury, these techniques should be instituted at the time of reperfusion. Experimental and perhaps clinical studies seem indicated and timely.

3) Myocardial ischemia

Although the coronary sinus techniques have been fully evaluated during myocardial infarction, their usefulness in the treatment of acute ischemia, analogous to the clinical setting of unstable angina or acute coronary insufficiency, has had limited investigation.
To determine whether PICSO might provide a simple and practical method of reversal and/or reduction in brief myocardial ischemia, Jacobs et al. (16) studied 9 open-chest anesthetized dogs. PICSO was performed using a pump inflated balloon tipped catheter in the coronary sinus until coronary sinus occlusion pressure reached a plateau (10 seconds). The balloon was then rapidly deflated (2 seconds) and the cycle repeated. Regional left ventricular function in the ischemic zone was assessed by sonomicrometry. Coronary blood flow was measured with a flow probe around the left anterior descending artery proximal to an occluding suture. An electrocardiogram was recorded from precordial leads. Measurements were obtained at baseline, during a 3 minute coronary artery occlusion and for 30 minutes of reperfusion. After return to baseline, PICSO was instituted for 15 minutes and continued during a second 3 minute coronary artery occlusion and 30 minutes of reperfusion. In an additional 5 dogs, this sequence was repeated during an infusion of Adenosine at a dose which abolished reactive hyperemia following coronary artery occlusion. During coronary artery occlusion, mean ST segment elevation and reduction in left ventricular shortening and thickening were not affected by PICSO and left ventricular functional recovery time was unchanged during PICSO (Tables 1 and 2). Although the hyperemic response in coronary blood flow following release of coronary artery occlusion was blunted by PICSO, coronary blood flow was also reduced by PICSO during Adenosine infusion, prior to coronary artery occlusion.
The authors concluded that in this model, PICSO does not prevent, reduce, or shorten the response to brief ischemia. Since PICSO also reduced coronary flow during Adenosine prior to coronary artery occlusion, the reduction in hyperemia during PICSO is likely to be the result of mechanical factors arising from venous engorgement, rather than to a decrease in the ischemic stimulus which causes vasodilation.
These data support the mechanism of action of PICSO as postulated and supported by Mohl (26). Periodic occlusion of the coronary sinus produces venous engorgement and redistribution in venous flow toward the ischemic area; the venous capacitance system should be filled when coronary sinus occlusion pressure reaches a plateau. Hence, the term "pressure controlled". Coronary sinus release then facilitates a washout phenome-

Table 1. Effect of PICSO during reperfusion.

	End-diastolic length		End-systolic length	
Time	– PICSO	+ PICSO	– PICSO	+PICSO
3' occlusion	125 ± 19	119 ± 17	152 ± 31	150 ± 28
1' reperfusion	95 ± 6	100 ± 18	94 ± 14	95 ± 11
2' reperfusion	97 ± 9	100 ± 19	93 ± 11	93 ± 8
3' reperfusion	100 ± 9	96 ± 3	98 ± 11	95 ± 7
4' reperfusion	101 ± 7	99 ± 7	98 ± 10	96 ± 8
5' reperfusion	103 ± 8	97 ± 7	101 ± 8	97 ± 7
7' reperfusion	101 ± 3	97 ± 5	102 ± 6	98 ± 6
10' reperfusion	101 ± 4	99 ± 8	101 ± 8	100 ± 6

percent of baseline, mean ± SD

Table 2. Effect of PICSO during reperfusion.

	End-diastolic thickness		End-systolic thickness	
Time	– PICSO	+ PICSO	– PICSO	+PICSO
3' occlusion	91 ± 5	93 ± 11	83 ± 10	81 ± 13
1' reperfusion	110 ± 6	116 ± 9	119 ± 4	111 ± 17
2' reperfusion	111 ± 9	113 ± 8	115 ± 5	117 ± 10
3' reperfusion	110 ± 6	110 ± 9	111 ± 5	111 ± 6
4' reperfusion	107 ± 5	107 ± 9	106 ± 6	107 ± 4
5' reperfusion	105 ± 7	105 ± 8	103 ± 7	106 ± 4
6' reperfusion	105 ± 6	104 ± 9	100 ± 7	103 ± 4
10' reperfusion	103 ± 5	104 ± 9	98 ± 7	99 ± 5

percent of baseline, mean ± SD

non whereby myocardial edema and toxic metabolites accumulated during ischemia are drained. It follows that PICSO would reduce cell necrosis if performed during an evolving myocardial infarction. However, in this model of ischemia, too brief to result in edema formation, the beneficial effect of PICSO may not be apparent.

Mohl and colleagues (29) evaluated the role of PICSO in a model of "chronic" ischemia, testing the hypothesis that the salutory effect of PICSO would be enhanced in the presence of a partially filled microcirculation. In 6 open-chest anesthetized dogs, left anterior descending coronary artery flow was reduced in stepwise fashion until it was less than 10 percent of the baseline control value and significant left ventricular dysfunction was achieved. After the ischemic segment exhibited stable dysfunction, PICSO was started (balloon inflation 25 ± 3 seconds, balloon deflation 4 ± 2 seconds) and maintained for 10 ± 3 minutes. Measurements of left ventricular function, as assessed by sonomicrometry, were obtained at the end of the treatment period during coronary sinus occlusion (balloon inflated approximately 20 seconds) and compared with those obtained during ischemia before PICSO. Myocardial segment shortening in the ischemic zone was de-

creased from a pre-ischemic baseline level of 14.0 ± 2.4 to 5.5 ± 1.2 percent. Ischemic segment shortening improved slightly during a 10 minute application of PICSO to 8.9 ± 2.6 percent (P = NS). Interpretation of this preliminary data is difficult due to the small number of dogs. In addition, it may be more physiologic to average measurements of left ventricular function throughout the PICSO cycle, rather than to assess shortening only during coronary sinus occlusion.
Therefore, review of the experimental data investigating the effect of coronary sinus technique during acute ischemia suggests that PICSO may have a limited role in this setting. However, evaluation of coronary sinus interventions in a "demand" model of ischemia (i.e. pacing induced ischemia in the presence of a fixed coronary stenosis), a model more analogous to human atherosclerosis, seems warranted.

4) Retroinfusion

a) Delivery of cardioplegic solution:
Retrograde coronary sinus perfusion (retroinfusion) has undergone extensive laboratory and clinical evaluation. As early as 1956, Lillehei et al. (20) used hypothermic retrograde coronary sinus perfusion as the method of protection during aortic valve surgery. The growth and development of antegrade delivery of cardioplegic solutions then emerged in the field of myocardial protection until the 1970s when several investigators (21, 31) reported on the efficacy of retrograde coronary sinus perfusion in providing myocardial protection during global ischemia. In 1982, Menasche and colleagues (26) performed a prospective evaluation of patients undergoing aortic valve replacement receiving either antegrade or retrograde potassium hypothermic cardioplegia as the method of myocardial protection. The authors concluded that retrograde perfusion was associated with a lower incidence of myocardial damage and improve postoperative left ventricular function. In 1984, after evaluating the effects of blood cardioplegia delivery via the aortic root versus via the coronary sinus on myocardial compliance in 10 dogs with coronary artery occlusion, Gundry et al. (11) reported that cardioplegia via the coronary sinus offers superior protection of myocardial compliance distal to the coronary artery obstruction. Indeed, myocardial function distal to the coronary occlusion was preserved only in the presence of retroinfusion of the cardioplegia. Walter and colleagues (37) noted that retrograde coronary sinus perfusion with Bretschneider solution in patients undergoing aortocoronary bypass surgery was associated with a smaller degree of ultrastructural and biochemical ischemic surgery as compared to antegrade perfusion.
Additional studies have shown that myocardial hypothermia is more homogeneous with retrograde coronary sinus perfusion than with antegrade coronary artery perfusion in the presence of coronary artery narrowing or total obstruction (10). Although it has been shown that not all of the right ventricular venous drainage empties into the coronary sinus (2, 36) no large temperature gradients have been observed between the right and left ventricles. In addition, ultrastructural injury to the coronary venous system is minimized by appropriate control of pressure and flow rate.
Therefore, retroinfusion of cardioplegic solution appears to be a viable and promising technique in selected patients, in that it allows avoidance of trauma to the coronary arteries and may provide a more homogeneous distribution of cardioplegia distal to proximal coronary stenoses.

b) Retroinfusion of pharmacologic agents during SRP or PICSO:
Coronary sinus instrumentation provides an alternative route to deliver pharmacologic agents to otherwise poorly accessible myocardium distal to a coronary occlusion. Retroinfusion by SRP or during PICSO would, therefore, potentially salvage additional myocardium. In fact, Povzhitkov et al. (32) demonstrated that administration of Prostaglandin E_1 by SRP enhanced the effectiveness of SRP treatment of acute ischemic myocardium. In addition, Meerbaum and colleagues (25) showed that retrograde lysis of coronary artery thrombus by coronary venous streptokinase administration occurred sooner than with antegrade streptokinase administration and Karagueuzian et al. (19) noted that retroinfusion of procainamide was effective in the management of inducible ventricular tachyarrhythmias in conscious dogs.

5) Reperfusion following global ischemia

Despite current advances in techniques for revascularization of ischemic myocardium, the optimal management of the ischemically injured myocardium during reperfusion remains a significant clinical problem.
Many of the histologic and biochemical changes associated with ischemic injury of the myocardium show marked progression during post-ischemic myocardial reperfusion [34]. Although chemical cardioplegia and myocardial cooling during prolonged global ischemia have become widely accepted clinical techniques for protecting the heart during cardiac surgery, the arrested heart remains vulnerable to further injury during reperfusion. Numerous reperfusion solutions with metabolic substrates (12), mannitol (22) and calcium channel blockers (13) are under investigation in an effort to reduce "reperfusion injury".
Mohl and colleagues (27) have demonstrated that PICSO performed in the setting of reperfusion following global myocardial ischemia is both safe and feasible. In 9 patients undergoing coronary bypass grafting, PICSO was performed during the reperfusion period (40.4 ± 11.6 min) following aortic declamping and 6 patients served as controls. Serial blood samples were obtained to determine peak enzyme levels. During PICSO, there was an increase In CK, CK-MB and α HBDH as compared with controls. These very preliminary data suggest that PICSO may enhance washout of cytoplasmic enzymes. If, in addition, PICSO increases washout of cellular edema and toxic substances accumulated during ischemia, it would be a useful technique to perform during the reperfusion period. Additional studies evaluating a role for PICSO in this setting are under investigation.

6) Diagnostic potential of coronary sinus pressure

The hemodynamic components of coronary sinus occlusion pressure and the relationship of coronary sinus occlusion to coronary blood flow has been evaluated by Jacobs and colleagues (15). In an open-chest canine model, systolic coronary sinus occlusion pressure reflected aortic or left ventricular systolic pressure. This is not unexpected since during systole, with compression of the microcirculation, the venous system acts as a conduct to transmit systolic pressure. In contrast, diastolic coronary sinus occlusion pressure was

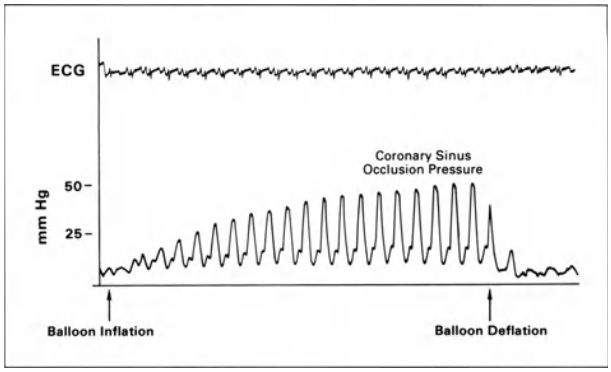

Fig. 3. Coronary sinus pressure. Inflation of the balloon on the tip of a catheter in the coronary sinus is followed by a rapid rise in coronary sinus pressure. When the coronary sinus is obstructed, coronary sinus occlusion pressure reaches a plateau. Deflation of the balloon is followed by a prompt decline in coronary sinus pressure back to baseline.

higher than diastolic left ventricular pressure but lower than aortic diastolic pressure. This diastolic pressure difference suggests venous outflow through other channels. While the coronary sinus occlusion pressure was unrelated to coronary blood flow, the rate at which it reached its plateau following occlusion was related with the rate of rise of coronary sinus pressure (Fig. 3) increasing from 23 ± 15 mm Hg/second during baseline conditions to 31 ± 15 mm Hg/second during Adenosine infusion. This increase in the rate of rise of coronary sinus occlusion pressure directly correlated with the increase in coronary sinus flow over a wide range of flow both at baseline and during Adenosine infusion.

Additional potentially useful information may be gained by evaluating the coronary sinus pressure wave form. If it is postulated that the plateau of the coronary sinus pressure represents filling of the venous system, then it follows that the rate of use of the pressure after the coronary sinus is obstructed and/or the height of the pressure may relate to the region at risk of infarction. That is, the larger the area distal to a coronary occlusion, the longer it would take to fill the empty venous vasculature once the coronary sinus is occluded. Indeed, in preliminary studies by Aigner et al. (1) it has been shown that coronary sinus occlusion pressure in systole and diastole is a complex function which is related to risk region following coronary artery occlusion.

The evaluation of the hemodynamic correlates of coronary sinus occlusion pressure has been performed in humans by Faxon et al. (9). In 27 patients undergoing diagnostic cardiac catheterization, a 7F balloon-tipped catheter (Swan-Ganz thermodilution catheter, n = 15; Baim coronary sinus thermodilution catheter, n = 12) was positioned in the coronary sinus under fluoroscopic guidance and pressure monitoring. The position of the catheter was verified by injection of angiographic contrast media during fluoroscopy. Coronary sinus occlusion was accomplished by sudden inflation of the balloon with 1.5 cc of air. Coronary sinus pressure was continuously recorded before, during and after brief occlusions of the coronary sinus for 20 seconds. Simultaneous recording of aortic and left ventricular pressure was also obtained.

Following inflation of the balloon, the rise in coronary sinus pressure occurred within the first 2 to 5 cardiac cycles and then assumed a plateau. The contour of the diastolic pressure closely resembled the diastolic pressure within the left ventricle. Statistically, no significant difference was noted between the diastolic coronary sinus occlusion pressure and the left ventricular diastolic pressure either early, prior to the A wave, at the A wave or at end-diastole. The most consistent relationship between the pressures occurred at the end

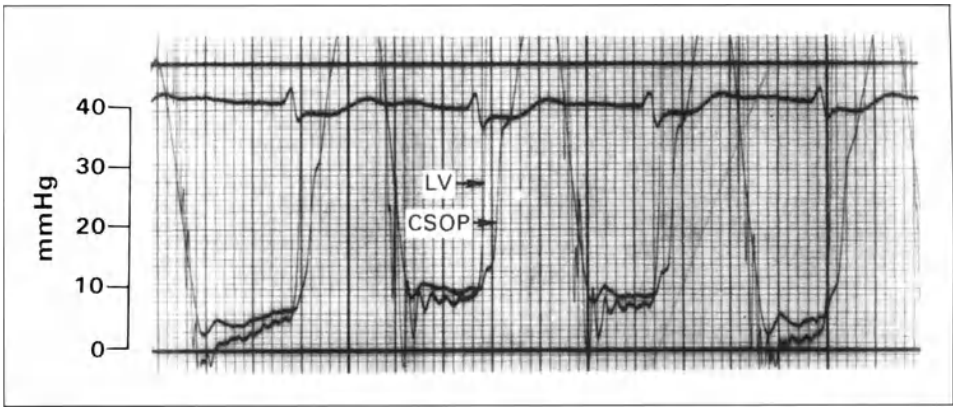

Fig. 4. Simultaneous recording of left ventricular diastolic and coronary sinus occlusion pressure in a patient with severe mitral stenosis and atrial fibrillation showing a close relation between diastolic left ventricular pressure and diastolic coronary sinus occlusion pressure.

of diastole with a close correlation between left ventricular end-diastolic pressure and end-diastolic coronary sinus occlusion pressure ($r = 0.85$, $p < 0.001$). In 4 patients with mitral stenosis and atrial fibrillation, the coronary sinus pressure in diastole closely followed the left ventricular end-diastolic pressure despite changes in R-R intervals and in the height of the left ventricular end-diastolic pressure (Fig. 4).

While the diastolic pressures correlated closely, the coronary sinus systolic pressure was significantly lower than left ventricular systolic pressure and no consistent relationship occurred between them. The close relationship of pressure during diastole, unlike the relationship in dogs, supports the concept of a more extensive Thebesian circulation drainage into the left ventricle.

Of importance is that this study demonstrates that the measurement of coronary sinus occlusion pressure in man is both safe and feasible. The indirect assessment of left ventricular end-diastolic pressure via the coronary sinus may prove a useful way to monitor critically ill patients and assess cardiac function. The experimental studies suggest that measurement of the rate of use of coronary sinus occlusion pressure may indirectly assess coronary blood flow. In addition, analysis of coronary sinus occlusion pressure during acute myocardial infarction may be a useful index of the efficacy of therapeutic interventions such as PICSO.

Conclusion

Coronary sinus techniques appear to be a sound and promising modern day extension of Beck's surgical procedure. We look forward to clinical studies over the next few years which are likely to delineate a role for these procedures in the temporary treatment of acutely ischemic myocardium.

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The promise and limitations of coronary venous retroperfusion: lessons from the past and new directions

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Coronary venous retroperfusion appears to be approaching an important turning point. Taking advantage of new methods and measurements, and building upon extensive past studies, we are witnessing an intensification of research and development. We are on the threshold of important new clinical and surgical trials. While there is certainly no shortage of questions about mechanisms, and indeed reports on limitations of the procedure, it is now recognized that retroperfusion can represent an effective support or essential treatment in particular circumstances refractory to other medical or surgical approaches. If the history of coronary artery bypass can be a guide, substantial application need not and should not diminish committed research efforts. On the contrary, it should encourage intensification of investigations so as to improve understanding and achieve optimization of the technique. Whereas scientific advances are generally derived from a succession of observations, any one of which may not be quite unique, pioneering progress is probable when the significance of past findings is fully understood, and then, of course, acted upon. The following survey will aim at reviewing the past work and, hopefully, crystallize significant issues still awaiting resolution. The amount and diversity of past studies in this field is truly striking. I wish to express my respect to all the past investigators, and offer apologies to those not included in this review. To meet the challenge of the survey, the literature will be divided into the following categories: I. Coronary venous anatomy and drainage patterns; II. Coronary venous physiology and effects of manipulations; III. Recent development of an intermittent coronary sinus occlusion technique; IV. Past and renewed surgical retroperfusion methods; and V. Development of clinically oriented retroperfusion techniques.

I. Coronary venous anatomy and drainage patterns

As early as 1708, Thebesius (115) injected dye into coronary veins and studied their drainage, some of which enters the cardiac chambers. Studies of the Thebesian circulation were pursued by Abernathy (1) in 1798, Langer (72) in 1880, and Pratt (95) in 1898. In 1928, Wearn (119) used retrograde injections and serial sections to demonstrate communications between the larger coronary veins and Thebesian veins. Grant (47) injected saline or chrome yellow gelatin into coronary veins at a low pressure of 20–50 mm Hg, and found effluent to issue from Thebesian orifices into both ventricles as well as efflux from coronary arteries adjacent to the veins. Katz (66) found the outflow by the drainage channels (coronary sinus, Thebesians and right heart veins) to be widely variable. Thus,

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drainage by the coronary sinus alone varied from 17–44% (average 32%). Similarly, Lendrum (73) listed drainage directly into the coronary sinus as 36.4%, compared to 24.5% directly into the right atrium, 30.8% into the right ventricle, 1.4% into the left atrium and 7.3% into the left ventricle. Prinzmetal (96) utilized radioactive erythrocides and glass spheres, and established the existence of arterial-venous anastomosis.

Gregg (48) performed, in 1947, a classical study of the coronary venous drainage in anaesthetized open chest dogs. Blood flow measurements indicated, as expected, that the right coronary artery is the major source of blood supply of the right ventricle and the anterior cardiac veins its major drainage system. The left coronary artery and the coronary sinus with its contributing veins constitute the corresponding arterial and venous systems of the left ventricle. The superficial veins of the heart appeared to play the dominant role in draining the coronary vascular bed, and the two coronary venous systems featured many anastomoses, those between the anterior cardiac veins and those contributing to the coronary sinus being particularly extensive. When either superficial coronary venous system was acutely blocked, the coronary inflow to the respective myocardium was usually only moderately reduced, and the venous blood presumably shifted to other unblocked venous channels. Gregg's observations offered little support for the belief that Thebesian vessels can serve in a major capacity as an alternative venous drainage. Watanabe (118) also estimated the proportion of the Thebesian, arterial-luminal and arterial-sinusoidal shunt flows, and found these to be only several percent of the total coronary flow.

Guglielmo (51) in 1951 studied the anatomy of coronary veins with more than 220 thoracic aortographies in 73 living dogs, and described changes in the coronary venous circulation caused by epinephrine and experimental infarction. Hellerstein (58) examined the anatomic variations of the orifice of the human coronary sinus and concluded that catheterization should be possible in 75% of cases. Gensini (43) presented in 1963 a detailed approach to clinical study of the coronary venous circulation and studied the anatomy of this circulation in the human. Friesinger (40) used the indicator dilution principle to study coronary blood flow and venous drainage, and Bartelstone (9) reported on partition of canine coronary blood flow during open chest right heart bypass.

Exemplifying studies needed in the human, the wife-husband team of Eliskova and Eliska (34) carefully evaluated the subepicardial veins of dogs' hearts and their anastomoses. They found the canine subepicardial venous system to form a widely connected network. The coronary veins often run in pairs along the arteries, and are frequently covered by muscle bridges along their course, particularly the middle cardiac vein. With the exception of the anterior cardiac veins, the veins are without macroscopic subepicardial fat. The diameters of the anastomosing branches rage from 0.1 to 1 mm (most often 0.2–0.3 mm) and numbered from 1–8 (mostly 2–3). Anastomoses are numerous between the great cardiac vein (62.5%), between the posterior and marginal vein (35%), the great cardiac vein to marginal vein (30%), and between the middle cardiac and posterior vein (30%). These authors also studied the arterial and venous circulation in ischemic regions of the myocardium.

Hood (62) studied 19 human hearts and found that the coronary sinus drains 96% of left ventricular and septal myocardium. Pakalska (92) examined 56 human hearts. She noted arterial-venous anastomosis in myocardium of 40 hearts, particularly in those with atherosclerotic coronary arteries, most frequently in the walls of the left ventricle and septum, less so in right ventricular walls. Farrer-Brown (38) found that in normal hearts large drainage veins began in the subendocardial zones and coursed fairly directly toward the

epicardium, maintaining a comparatively even caliber throughout. Similar but smaller drainage veins began in the middle of the myocardial wall. In the heart with severe generalized coronary artery atheroma, the normal pattern in the inner heart wall was replaced by a plexus of small veins, the majority of which coursed circumferentially. Olsen (88) reviewing the retrovenous arterialization of ischemic myocardium, felt in 1975 that the following questions still remained to be answered through anatomic and functional study: Where does the retroperfusate go? To what extent does retroperfusion create arterio-venous shunts? What alterations occur in the coronary vein and myocardium in the long term? Will collaterals develop from the venous system to other veins and/or the heart cavities?

In 1980, Lolley (74) performed an asanguinous retroperfusion of the coronary sinus, and found that it can penetrate a significant microvascular bed in proximity to myocardial cells. Myocardial regions permeated by this technique were located in the apex, septum, endocardium and free wall of the ventricle. Retrograde drainage patterns heavily favored the Thebesian-sinusoid system over the capillary-arterial route, by more than a 3 : 1 ratio. Microscopic India ink preparations, regional flow studies and retrograde roentgenograms indicated that asanguinous cardioplegic agents and core cooling can penetrate important regions of the heart at a microvascular level, and may thus be an alternative route when routine antegrade perfusion via the coronary artery is unavailable or disadvantageous. Hochberg (60), examining different modes of retrograde coronary venous perfusion, pointed out that valves at the orifice of major coronary veins could account for the failure of global arterialization and the experimental success of selective venous perfusion.

Comment: Coronary venous anatomy and drainage patterns are important determinants of retroperfusion effectiveness and further efforts should be directed toward improved definition of the geometry and resistance of particular intramyocardial and epicardial vascular pathways. As pointed out by James (63), although the venous flow from right ventricular myocardium is generally through the anterior cardiac vein and that of the left ventricular myocardium generally through the coronary sinus, there is no anatomic reason why with almost any increased resistance in either of these two venous systems, the flow could not go in the opposite direction via the large anastomosis. Due to the inevitable variability, appropriate monitoring and measuring techniques will have to be devised so that individual retroperfusion capacity can be assessed, by diagnosing the coronary venous pattern as well as the degree to which controlled injections can penetrate the microcirculation or else are shunted off via non-nutritional paths. More attention needs to be paid to coronary venous anatomy and anastomosis pertaining to left circumflex and right coronary dependent territories of the heart.

II. Coronary venous physiology and effects of manipulation

Ever since the 1930s, much debate has centered upon the effects of coronary venous obstructions. Gross (50) studied coronary sinus ligation in normal dogs, observed almost immediately a considerable dilatation of the veins and expansion of the vascular bed, but found such intervention generally salvaged infarct size following acute coronary artery occlusion. Gregg (49) noted the added consequence of moderate coronary inflow reduction, and reported that contraction of ischemic myocardium failed to benefit. Although

he did observe an increase in peripheral backflow from the occluded coronary artery, Gregg did not consider coronary sinus occlusion per se advantageous for retrogradely supplying a potentially infarcted area. Eckstein's (31) retrograde arterialization showed that flow from the sinus through capillaries supplied 14–25% or normal myocardial oxygen requirements. Nagy (87) localized receptors in the coronary veins responsible for the chemo reflex in the dog, but Moers (86) concluded that the cardiovascular reflex depression associated with coronary sinus occlusion was caused by intravascular pressures indirectly stimulating nerve endings in the ventricles of the heart.

More detailed studies of the coronary venous occluded pressure were those of Gensini (44) and DiGiorgi (29) who examined central and peripheral coronary veins and arterial pressure in relation to phasic coronary blood flow, as well as aortic, left ventricular, right ventricular and right atrial pressures. The coronary venous wedged pressure was said to be closely related to coronary venous blood flow and its phasic morphology. Scholtholt (103) measured in closed chest dogs a characteristic phasing of coronary venous outflow in relation to the cardiac cycle, with most outflow occurring in isotonic systole and the adjacent isovolumetric periods. Thus, little coronary venous drainage takes place in diastole, which Beck (12) called the optimal period for retroperfusion. Further physiologic studies of Bellamy (14), Armour (4), Klassen (69), Wong (121), Chilian (22) and Rouleau (100) are also of considerable significance since they studied coronary venous pressure-flow characteristics. However, their primary emphasis was on resolving the myocardial microvascular controversy relative to the vascular waterfall hypothesis.

A significant study by Cibulski (26) applied in dogs retrograde radioisotope injections into occluded coronary veins for study of myocardial perfusion patterns. In the presence of coronary artery obstructions, the radioisotope was found distributed mainly to the low pressure ischemic zones, the ratio of occluded-to-unoccluded area content being as high as 6 : 1. Potassium 43, Krypton 85 and 133 Xenon were employed by Cibulski, who concluded that such techniques may lend themselves to practical study of hypoperfused myocardial zones. Thus, effective retroperfusion techniques will concentrate retroperfusate in the most jeopardized ischemic area, and are also found to favor perfusion of the endocardial layer of myocardium. A less certain effect was dealt with by Ungerleider (117) who found that arterial collateral circulation to an ischemic region may at least sometimes be enhanced when the pressure in the corresponding veins is increased.

An important issue to retroperfusion relates to safety of a procedure which clearly institutes a modified state of myocardium and its circulation. The various studies in or about the Beck era indicated that peak coronary venous pressure should be limited to 60 mm Hg or less, with mean pressure preferably kept in the range of 30–40 mm Hg. More recently, Williams (120) demonstrated edema, hemorrhage and poor contraction of ex-vivo canine hearts during retrograde perfusion. The derangements could be overcome by phenoxybenzamine treatment for up to 1 hour, following which, however, contraction deteriorated. Edema and effects of myocardial stiffness were further studied by Pogatsa (93). Thatcher (114) and Toscano (116) provided evidence that a definitive limit must be set on retroperfusion-induced coronary venous pressures if damage is to be avoided, even during short applications. Thus, Toscano studied in pigs regional retrograde coronary venous perfusion via a surgical graft for prevention or treatment of coronary artery occlusion. When the coronary vein and ischemic myocardium were exposed to systemic pressures via the graft, one did observe reversal of mechanical and electrical indices of ischemia, but after several hours, myocardial edema and hemorrhage were evident, along

with increased infarction. In contrast, externally pumping blood via the graft to limit coronary venous blood pressure to 35–40 mm Hg avoided interstitial hemorrhage, limited infarction and maintained myocardial contraction. Non-invasive echo assessment of edema and abnormal contraction during coronary vein obstruction with patent coronary artery was reported by Jang (64). Yet another issue is potential coronary vein thrombosis as reported by Hazon (57).

Recently, several studies provided information on retroperfusion-induced changes in regionally ischemic myocardial metabolism. Thus, Taira (112) performed studies in isolated rat hearts by the Langendorff technique, and applied NADH fluorescence photography. This study found that retrograde coronary venous perfusion improved myocardial function and energy metabolism during acute coronary artery occlusion, but the retrograde supply of arterial blood to the acutely ischemic region was not sufficient to be reflected in adequate oxygen delivery and oxydative phosphorylation. The question of retroperfusion effects upon myocardial blood flow and the appropriate method for obtaining correct measurements remains unresolved. Studies by Chiu (24), Hochberg (61), Berdeaux (16) and others present a somewhat confusing picture in that admittedly different experimental retroperfusion protocols yielded data indicating either very limited (several %) or quite substantial (up to 50%) retrograde delivery of myocardial perfusion. Retrograde antegrade microsphere methods, procedures and factors influencing perfusion have yet to be critically evaluated.

Comment: The physiologic consequences and safety of coronary venous occlusion alone or with retrograde flow and arterialization are still not fully understood, and more research is needed even as applications proceed. Differences in species and normal vs. diseased states should be clarified. The coronary vein pressure-flow relationships in the absence or presence of interventions need to be defined for a variety of anatomic situations. The influence of chronic vs. acute effects must be clarified, in general and in relation to specific intravascular pressure-flow criteria to avoid vascular trauma, myocardial edema, hemorrhages and thrombosis.

III. Recent development of an intermittent coronary sinus occlusion technique

In 1977, Arealis (3) published an account of experiments in dogs and sheep, exploring whether blood supply to an acutely ischemic area of the myocardium can be increased by intermittent occlusion of the coronary sinus. The intermittent coronary sinus occlusion (ICSO) was accomplished with a latex balloon at the tip of a catheter, and equipment used to phasically drive the balloon was basically the same as that for intraortic balloon pumping. The balloon was inflated and deflated at a rate of 60/min. During ischemia, produced by sequential coronary branch occlusions, myocardial function deteriorated significantly. When ICSO was started, hemodynamics generally improved and irregular ischemic rhythm was normalized. In 85 episodes of stopping and restarting ICSO, a deterioration usually ensued upon stopping ICSO, while the acute distress due to coronary artery ligations could be acutely reversed by reestablishing ICSO. The ICSO coronary venous balloon phasing appeared to be best with inflation during 70% of the cardiac cycle vs. 30% deflation. The intermittently increased pressure of the coronary sinus was thought to cause blood to back up toward the ischemic area. Sinus balloon deflation was believed to enhance coronary venous drainage.

In 1984, Mohl (82) described the development of a simple pressure controlled intermittent coronary sinus occlusion (PICSO) technique aimed at protection of ischemic myocardium. He hypothesized two beneficial mechanisms: 1) redistribution of coronary venous blood flow from normal to compromised ischemic areas; 2) a forced "sweeping out" of toxic and edematous substances during the coronary venous drainage phase. The balloon occlusion vs. release phase was controlled in a feedback fashion by the coronary sinus pressure. In open chest dogs, left ventricle infarct size after 6 hours' occlusion was significantly reduced when PICSO was applied from 15 min post-occlusion onwards (19% vs. 31% in untreated controls). It was concluded that this retrograde intervention has clinical potential and could serve as an interim support to protect deprived myocardium. Myocardial metabolism (ATP, ADP) was also found to be improved. A report by Ciuffo (27) seemed to support the infarct salvage with PICSO, but Zalewski (125) found intermittent coronary sinus occlusion to be insufficient without arterialization to provide major myocardial protection.

Mohl's (83) measurements during coronary sinus occlusion indicated a sinus systolic mean pressure rise from 10 to 44 mm Hg, while the distal occluded coronary artery mean pressure increased in tandem from 22 to 30 mm Hg ($p < 0.05$). In view of initial favorable indications, Mohl carried out a further study to examine effects of PICSO on regional ischemic myocardial function. In 8 closed chest anaesthetized dogs, PICSO was applied for 2.5 hours between 30 min and 3 h of intravascular balloon occlusion of the proximal LAD. Standardized two dimension echo measurements of left ventricular function were performed to derive systolic fractional area change in short axis sections and subsegments at 5 levels of the left ventricle. At the most extensively involved low papillary muscle level, regional ischemic fractional area change was significantly but partly increased by PICSO between 30 and 180 min of LAD occlusion, from -4 ± 0.1 to $14.4 \pm 4\%$. This compared with persisting ischemic dysfunction or further deterioration in untreated dogs with equivalent coronary occlusion. The PICSO-induced recovery of cardiac function was attributed to enhanced ischemic zone washout.

In association with the above studies, Kenner (67) and Moser (85) developed techniques for measurement of the coronary circulation arterial-venous differences and gradients in blood density. The blood density was measured continuously and accurately using a mechanical oscillator technique. Arterial-venous density gradients were thus recorded in the coronary vascular bed of anaesthetized dogs to determine filtration and effects of intermittent coronary sinus occlusions. It was found that the coronary sinus blood has a higher density than arterial blood, due to the loss of filtered fluid in the microcirculation. The amount of fluid lost ranged from 0 to 10 ml/100 g/h, corresponding to myocardial lymph flow. Simple increase of the coronary venous pressure leads to an increase of the density gradient, but PICSO reduced or reversed the density gradient. This was attributed to a washout of fluid of relatively high protein content, as the changing gradient was not observed in the arterial-venous plasma density determined from blood samples. It may be presumed that PICSO institutes enhanced myocardial washout of metabolites and that this process could be responsible for the reported benefits to infarcted myocardium.

Comment: Intermittent coronary sinus occlusion represents an interesting concept, and the negative feedback feature of the pressure controlled intermittent coronary sinus occlusion system merits further investigation. In particular, this approach has brought to the forefront the question regarding the potential contribution of myocardial metabolite washout for improved tissue salvage and improved function during acute ischemia or

evolving myocardial infarction. Past fragmentary observations of benefits due to simple continuous coronary sinus occlusion have not been fully borne out, but the intermittency with optimized occlusion-release phasing should help, and perhaps a more regional coronary sinus site could also be beneficial. Finally, there is no fundamental reason why this technique should not be conceived of in broader terms, approaching other retrograde methods, such as temporary retroinfusion of pharmacologic agents for the coronary venous treatment of ischemic syndromes.

IV. Past and recent surgical retroperfusion methods

Pratt (95) is generally considered the originator of the retroperfusion concept since he reported in 1898 that he was able to maintain contractions in an isolated feline heart for 90 min by perfusing its coronary sinus with arterial blood. In the 1930s, Batson (10) postulated an ebb-and-flow coronary venous retrograde circulation during coronary artery occlusion, Gross (50) noted increased ischemic animal survival with partial coronary sinus ligation, and Gregg (49) observed an elevated occluded LAD back flow following coronary venous ligation. Beck (11) found in animals with up to 4 months coronary sinus ligation that mortality associated with LAD obstruction was reduced and infarct size decreased. With this as background, Roberts (98) introduced in 1943 systemic arterial blood into the coronary sinus of dogs and was able to maintain contraction in the canine heart for 26 h following ligation of the coronary arteries.

The Beck period. Beck (13) accomplished coronary sinus arterialization by a graft from the aorta to the sinus, and found it physiologically effective. He considered the arterial supply to the sinus a primary retroperfusion requirement and also urged careful attention to safe methods by which blood is introduced into the coronary vein and optimization of the retrogradely delivered flow, along with a safety ceiling. A high flow into an occluded sinus may develop excessive pressures, causing vascular trauma, edema and myocardial damage. Conversely, while the variable and extensive veno-venous communications could serve as a relief valve and provide more comprehensive flow distribution, Beck recognized that these shunts can drain off the retroperfusate to an extent where little retrograde flow will enter the capillary bed of the jeopardized myocardium. His initial procedure used coronary vein ligation, but this was subsequently changed to partial sinus obstruction which yielded improved safety and more substantial infarct salvage.

Beck's contemporary investigators made many important contributions in the early 1950s. McAllister (77) used a 3.5–4 mm graft between the aorta and coronary sinus, and found that full coronary sinus ligation caused excessive pressures which led to cardiac failure, myocardial hemorrhage, and scarring and eventual graft thrombosis. Eckstein (31, 33) studied sinus occlusions and also mortality rate in dogs following acute circumflex artery occlusion with coronary sinus arterialization and mean sinus pressure held at 50 mm Hg. Within one hour, untreated occlusion resulted in 70% mortality, while all retroperfused dogs survived. After similar observations, Smith (108) concluded that achieving chronic effectiveness with retrograde arterialization will require limited elevation of coronary sinus pressures. Bailey (6) presented some evidence that arterialization of the sinus brought about in time dilatation of communications between epicardial veins of the left heart and the small veins of the right ventricle. Eckstein (32) and Bakst (7, 8) performed long-term studies on dogs with up to 1 year of a Beck coronary sinus

anastomosis, with sinus constriction and circumflex coronary occlusion. Their results indicated that the graft satisfactorily perfused the capillary bed of the occluded circumflex territory for several weeks after the operation, but then lost its functional contact with the capillary bed. The loss of longer term retrograde myocardial protection and increased mortality was due to marked intimal proliferation and thrombosis which developed within the major coronary veins. In the early phase when the graft was open, Bakst found that retrograde circumflex coronary artery blood flow was significantly increased and venous in character, yet after 1 year, the retrograde blood was found arterial in nature, probably reflecting increased intercoronary arterial collateral circulation. Thus, eventually, retroperfusion no longer contributed and appeared dispensible.

Beck and Leighninger (12) reported on a total of 186 patients with coronary artery disease treated with retroperfusion. Whereas the exact circumstances and results remain unclear, mortality was considered too high (10–26%) and the procedure was eventually abandoned at a time when the new coronary artery bypass operation commanded all the attention. Gott (46), among others, performed surgical retroperfusion in patients for direct vision aortic valve surgery.

Search for improved surgical retroperfusion. The literature of the 1960s indicates only minor activity in retroperfusion, possibly because investigators were consolidating past lessons or searching for new approaches. Camishion (20) perfused animal hearts in situ with gaseous oxygen through the coronary sinus during inflow occlusion, and found that the heart beat could be maintained for up to 7 hours. With oxygen tension of the myocardium maintained at an average of 450 mm Hg during retrograde oxygen perfusion, hearts of pigs and dogs with pulmonary bypass and proximal coronary artery occlusion exhibited only one case of post-operative heart failure. Hammond (55, 56) assessed myocardial function and oxygen utilization in normothermic or moderately hypothermic dogs undergoing left coronary artery occlusion and retrograde arterial blood perfusion, and found an acceptable post-operative myocardial function. In animals with bypass, Davies (28) used retrograde coronary sinus flows averaging 30–40 cc/min at a mean pressure of 35 mm Hg, since higher flows and pressures tended to cause vascular damage without significant increments in retroperfusion effectiveness. All retroperfused animals came off the bypass and showed excellent ventricular function postoperatively.

In light of difficulties with global coronary sinus retroperfusion, attributed by Hochberg (59) in part to coronary venous anatomy and valves, attention turned in the early 1970s to more regional surgical retroperfusion. To ameliorate acute ischemic changes, Sallam (101) used in experimental animals the internal mammary artery to perfuse a proximally ligated regional coronary vein. Signs of ischemia disappeared over a retroperfusion period of 25 min, and ischemia returned when the internal mammary graft was clamped. Similar studies were performed by Andreadis (2) who created an experimental aorto-regional coronary vein anastomosis. Gardner (41) arterialized the canine anterior interventricular vein (AIV); he found in the occluded LAD area a lowering of retroperfused blood oxygen content and myocardial uptake of 131 I macroaggregate albumen, and concluded that retrograde flow did perfuse the myocardium, although the possibility of small shunts could not be excluded. Bhayana (5) ligated the LAD in sheep and observed marked ST changes in the epicardial electrocardiogram. When the accompanying AIV was perfused with 20–90 cc/min blood via the internal mammary artery, ST changes became minimal. ST elevations indicative of ischemia reappeared when retroperfusion was stopped.

Park (90) reported good results in 6 patients in whom the left internal mammary artery was anastomosed to the left anterior coronary vein to provide myocardial retroperfusion, a procedure he proposed for patients with diffuse atheroslcerosis and poor or no distal coronary arterial runoff. Benedict (15) reported on 18 dogs and 3 clinical patients in whom he applied grafts from the aorta to the regional cardiac veins. The 3 retroperfused patients survived and were partially relieved of ischemic symptoms. In the animals, Benedict performed graft flow measurements, myocardial radionuclide scanning, hydrogen electrode study of shunting, coronary cineangiograms and methylene blue study of myocardial zones. His experimental study consistently demonstrated effective myocardial revascularization through the coronary venous system. Moll (84) reported the largest number of clinical cases since the Beck period. Over a 5 year period, up to 60 patients suffering from ischemic heart disease were treated with global and regional retroperfusion. Overall mortality was 7% and postoperative incidence of myocardial infarction was 11%. Examination 6 months after operation showed a 75% bypass patency. Proliferative venous bypass changes were noted in 10% of the cases. Kay (68) cautioned that although retrograde bypass perfusion seems appealing, the likelihood of success may be small since retroperfusion in opposition to residual antegrade perfusion causes the myocardium to become hemorrhagic. He proposed separate venting of the arterial side to a low pressure system.

Divergent evidence and conclusions. Limitations of the retroperfusion technique were noted by Chiu (24, 25) who studied selective arterialization of coronary veins during LAD occlusion. He did find in canines and sheep that arterial blood can be delivered promptly to regional myocardium without causing myocardial edema and hemorrhage. Infarct size was decreased, but focal transmural infarcts were observed near the apex of the heart. The retrograde blood flow exhibited a predominantly diastolic flow pattern. Studies with 15 micron radioactive microspheres revealed that capillary microsphere trapping was much less with retrograde coronary vein than with antegrade coronary artery injections, indicating significant "shunting" loss. Zajtchuk (124) perfused the AIV by the internal mammary artery in 56 dogs with normal or ligated LAD and found the protection to be of short duration due to eventual intimal fibrosis and luminal obstruction of the perfused veins, marked congestion of the myocardium and petechial hemorrhages. Solorzano (110) studied retrograde coronary sinus perfusion in a vented nonworking heart, and estimated the fraction of nutritional blood flow by 15 micron microsphere trapping to be about 20% of the total flow. Microfil injection study indicated a shunting runoff, primarily through Thebesian and veno-venous channels. These results suggested a marginal value in retrogradely revascularizing a working heart, but potential effectiveness in protecting a hypothermic non-working myocardium. Rhodes (99) evaluated dogs with aorto-great cardiac vein arterialization. Coronary vein occlusion alone actually decreased mean myocardial blood flow, although increasing its distribution to endocardium. Retroperfusion of acutely ischemic myocardium was found to be only partly effective in terms of restoring the decreased nutritional myocardial blood flow.

Others presented somewhat more favorable results. Thus, Schultz (104) evaluated 44 normothermic dogs fibrillated during cardiac pulmonary bypass, and measured oxygen uptake, vascular resistance, venous outflow and venous oxygen levels during a 1 hour 100 cc/min perfusion via the coronary sinus, following a 30 min anoxia. This study concluded that retroperfusion represents a surgically feasible technique for providing oxygen delivery to ischemic myocardium. Marco (75) provided in dogs with acute right heart by-

pass an internal mammary anastomosis to the AIV. An untreated LAD occlusion resulted in significant decline in stroke work, coronary flow and myocardial oxygen uptake. Whereas retroperfusion did not change these variables greatly, dogs with 6 weeks coronary vein arterialization exhibited minimal infarction and a 14% mortality, vs. 40% in controls. Marco concluded that venous arterialization does provide protection for ischemic myocardium, but observed that its effect may not persist long because of anastomotic occlusions due to fibrous proliferation. In an experimental study, Hochberg (61) evaluated in dogs with proximal LAD occlusion the long-term effectiveness of a saphenous vein interposed between the aorta and the AIV, the latter being ligated cephalad to the graft to prevent an arterial-venous fistula. Operative graft flow averaged 53 ml/min and most of the dogs catheterized after 3–5 months showed graft flows averaging 50 ml/min. Radionuclide microsphere based transmural myocardial flow to the retroperfused anterior wall was 39 ml/min/100 g, with an endocardial/epicardial flow ratio of 1.4. Upon graft ligation, myocardial blood flow dropped to 15 ml/min/100 g. In 19 control dogs, none of which survived more than 5 days, normal mean anterior wall flow was 100 ml/min/ 100 g, which decreased to 13 ml/min/100 g after ligation of both the LAD and AIV. Histologic examination disclosed that the longer term retroperfusion caused no venous sclerosis or thrombosis and no evidence of interstitial edema or hemorrhage was found. Regional retroperfusion appeared to facilitate long-term survival of severely jeopardized ischemic myocardium, and especially the subendocardium.

Retrograde cardioplegia. Attention in the 1980s turned to the use of retrograde coronary sinus delivery of cardioplegia. Thus, Bolling (19) investigated whether low pressure perfusion of the coronary sinus could deliver cardioplegic solutions beyond a coronary obstruction, providing myocardial preservation. He subjected 41 canine hearts to 90 min ischemia and circumflex coronary artery occlusion. One group received aortic root crystalloid cardioplegia, another group had supplemental topical cooling, while a third received continuous retrograde perfusion and a fourth retrograde oxygen perfluorocarbon. All solutions had a pO_2 of 400–500 mm Hg. In the first two groups, isovolumic developed pressure 1 h following reperfusion returned to 36 and 41% of preischemic levels, whereas the two retrograde groups featured a significantly greater recovery to 78 and 73% of control. During the ischemia, circumflex artery intramyocardial pO_2 fell and cooling was deficient with antegrade cardioplegia, while both retrograde methods maintained pO_2 and provided adequate uniform cooling. Others, including Chiu (23) and Sallam (101) confirmed that retrograde coronary sinus perfusion with a cardioplegic solution can be beneficial in the presence of occluded coronary arteries.

Gundry (52) used temperature mapping and sonomicrometry in the distributions of the LAD and circumflex coronary arteries, to study cold (4 °C) cardioplegia delivered through the aortic root vs. the coronary sinus. In dogs placed on cardiopulmonary bypass and cooled to 28 °C, the aorta was cross-clamped for 2 h with the LAD coronary artery occluded. During ischemia, aortic cardioplegia provided poor cooling distal to the coronary obstruction, and poor return of cardiac function, along with loss of compliance. Coronary sinus cardioplegia on the other hand, resulted in uniform and adequate myocardial cooling, good return of function, and normal compliance. He concluded that cardioplegia administered through the coronary sinus preserved myocardial function in all areas. Schwarke (105) increased coronary sinus pressure briefly during cardioplegia injection, and observed that this resulted in significantly improved flow of the solution through the myocardial capillary bed, and better myocardial protection.

Silverman (106, 107) instituted in dogs coronary artery stenosis to impede antegrade delivery of cold potassium cardioplegia via the aortic root, and examined the efficacy of retrograde cardioplegia via the coronary sinus. Transmural biopsy of both ventricles were assayed for ATP and CP, and regional wall temperatures were monitored. With and without LAD occlusion, the mean arrest time from aortic cross clamping was 174 or 175 sec, depletion of ATP as well as CP was comparable, and mean myocardial temperatures during the arrest were similar (17.2–19.5 °C). These recent data suggested that myocardial protection through coronary sinus retroperfusion was independent of arterial patency, perhaps provided some retrograde cooling, however this type of cardioplegic retroperfusion was deemed suboptimal due to the prolonged time needed to induce ventricular arrest. Fabiani (35) in a somewhat different approach, investigated retrograde coronary sinus cardioplegia by delivery into the right atrium after caval and pulmonary artery occlusion. He concluded that this technique might be safer and easier to perform than coronary sinus cardioplegia.

Coronary sinus cardioplegia has been used in patients during aortic valve surgery, in which antegrade cardioplegia might cause intimal injury and acute dissection. Thus, Menasche (81) evaluated retrograde cardioplegic perfusion in 12 patients undergoing aortic valve replacement. A balloon tipped catheter was inserted into the coronary sinus through the right atrium, and perfusion pressure averaged 40 mm Hg. Another 12 patients underwent the antegrade coronary cardioplegia. Postoperative evaluation focused on serial measurements up to 24 h of chamber pressures, cardiac output, stroke volume and the ventricular stroke work. Since retrograde coronary sinus perfusion proved simple and safe, and there were no statistically significant differences between the two groups, Menasche concluded that retrograde cardioplegia provides effective protection during aortic valve surgery. In a similar study, Takahashi (113) performed retrograde coronary sinus perfusion for myocardial protection, and found that cold blood or cardioplegic retroperfusion was a superior alternative myocardial protection technique, in addition to providing excellent operative exposure in aortic valve surgery.

Comment: In view of the widespread acceptance of the coronary artery bypass treatment, one might wonder if any other surgical technique is really needed. Yet, as more difficult cases of ischemic heart disease are included for potential treatment, aorta-to-regional coronary vein bypassing may remain of interest in the setting of diffuse coronary artery disease, particularly if improved methods can be devised to limit pressures in the coronary veins and maintain graft patency. Retroperfusion of cardioplegic agents has the potential of providing more uniform temperatures and improved return of myocardial function, but the unacceptable delay to arrest must be reduced. Coronary venous retroperfusion can also play a role in supplying a circulatory support and maintaining viability during ischemic periods preparatory to definite surgical or nonsurgical interventions, as well as pending achievement of fully effective reperfusion.

V. Development of clinically oriented retroperfusion techniques

Several reports in the 1960s concluded that it might be feasible to develop retrograde coronary venous perfusion into a clinically applicable emergency temporary revascularization of ischemic myocardium. This concept was articulated by Gensini (45) and Hammond (56) who studied retrograde coronary sinus perfusion in the dog during left coro-

nary artery occlusion. Rassman (97) also proposed acute revascularization of the heart through an occluded coronary sinus without thoracotomy. He examined retroperfused dog mortality during left circumflex coronary ligation and found it to be zero compared to 50–60% for untreated controls. Retrograde circumflex flow was significantly elevated by retroperfusion and dye injections demonstrated a favorable redistribution of myocardial flow. Although myocardial contraction was not enhanced, Rassman thought that the retrograde procedure with fluoroscopic control could be readily utilized in the coronary care unit for treatment of acute myocardial infarction. Spann (111) retrogradely perfused a balloon-occluded coronary sinus of dogs with oxygenated blood at systemic pressure, during total left coronary artery occlusion. Cardiac contraction was maintained while mean aortic pressure decreased 24 mm Hg, compared to significant deterioration of ischemic function without retroperfusion during 12 mm Hg reduction of blood pressure. Retroperfusion prevented ventricular fibrillation, which occurred in 33% of the controls. Spann concluded that this technique merits clinical trials.

Research and development accelerated in the 1970s. Wiener (122) observed a reversal of acute myocardial ischemia by retrogradely shunting blood from the carotid artery into the anterior interventricular vein during a LAD coronary artery occlusion. Myocardial tissue oxygen returned to normal, contraction normalized and there were no arrhythmias. Lolley (74) examined retrograde gravity perfusion during 30 min of arrest with a solution containing glucose, insulin and potassium. This resulted in significant utilization of glucose through retrograde capillary perfusion which was about one third of the non-nutritional Thebesian-sinusoidal shunting. Cardiac output, contraction and cardiac rhythm were all significantly better with retroperfusion than in a control series. This suggested an alternate mode of retrogradely supplying energy substrate when it is urgently required. Markov (76) used the coronary venous retroperfusion system during coronary artery occlusion in closed chest dogs, and was able to reverse or reduce manifestations of acute myocardial ischemia over a period of 30–60 min. Meerbaum (78) reported on an ECG-synchronized diastolic coronary venous retroperfusion technique designed to optimize delivery into acutely ischemic myocardium and also facilitate systolic drainage to avoid vascular trauma, edema and hemorrhages. A study in open chest dogs during LAD occlusion indicated that diastolic retroperfusion significantly improved regional cardiac contraction, reduced ischemic ECG-ST elevations and corroborated retrograde delivery to jeopardized myocardium.

Carabello (21) examined the potential of retrograde coronary venous perfusion of oxygenated blood for prevention and reversal of cardiogenic shock, modeled in dogs by acute ligation of the circumflex and LAD coronary arteries. When total left coronary occlusion was accompanied by simultaneous retroperfusion, cardiac output and systemic blood pressure were maintained, but fell drastically within 2 minutes when the retrograde treatment was terminated. All animals undergoing an untreated left coronary ligation died within 5 minutes from ventricular fibrillation, while this occurred in only 1 of 10 retroperfused animals. Carabello concluded that the prompt retrograde perfusion can prevent the development of cardiogenic shock in a working canine heart. Feola (39) used a double lumen balloon-tipped catheter inserted transvenously into the coronary sinus, with the balloon connected to a counterpulsing pump. Oxygenated blood was pumped continuously into the coronary sinus with a pressure of 50–75 mm Hg. The balloon was inflated in diastole, facilitating retrograde perfusion, and deflated during systole to prevent venous congestion. Open chest dogs had 15 minutes' proximal LAD occlusion followed

by 30 min retroperfusion during maintained LAD occlusion. Reduction of myocardial oxygen tension and ECG-ST elevations, which characterized the acute ischemia, were reversed by retroperfusion. There was no intramyocardial hemorrhage. Feola was encouraged, but wondered how long these beneficial effects could be maintained. Farcot (36) applied diastolic retroperfusion to closed chest dogs. The catheter-pump system consisted of an ECG synchronized retroperfusion pump and an auto-inflatable bladder catheter designed to both occlude the coronary vein during diastole, thus promoting arterial blood retroperfusion, and to facilitate systolic coronary venous drainage during balloon deflation. Dogs with 4 h LAD occlusion were treated during the last 3 h with diastolic retroperfusion. Hemodynamics and left ventricular function were improved, myocardial metabolism enhanced and infarct size significantly lowered compared to untreated controls.
Further corroborations of diastolic retroperfusion were reported. Berdeaux (16) examined the effects of diastolic retroperfusion on regional coronary blood flow during experimental myocardial ischemia. During a 2 hour LAD coronary artery occlusion, one hour of diastolic retroperfusion restored regional myocardial blood flow to approximately 50% of normal, and significantly increased the endocardial-to-epicardial flow ratio in the jeopardized region from 0.46 to 0.64. Berdeaux concluded that a substantial portion of the retroperfused arterial blood reaches the ischemic zone and is favorably redistributed toward the endocardium, which should be of value in delaying irreversible damage. Smith (109) and Geary (42) studied baboons in which the proximal LAD was occluded for 4 h and diastolic retroperfusion (40–50 ml/min) instituted 15 minutes or 1 hour after occlusion, followed by antegrade reperfusion up to 24 h. Smith found only 4.8% of the left ventricular mass infarcted and the percent underperfused risk zone necrosis in Geary's retroperfused animals was 57%. This compared with 31% left ventricular infarction and 94% risk zone necrosis in controls. This demonstrated the effectiveness of coronary venous retroperfusion in preserving ischemic myocardium, thus promoting effective reperfusion. Gundry (53) investigated diastolic retroperfusion of ischemic myocardium in normal and hypertrophied dogs. The LAD coronary artery was occluded for 40 minutes; early post-occlusion measurements indicated a severely depressed left ventricular function. Retroperfusion between 10 and 40 min post-occlusion restored 37% of systolic shortening, whereas there was no restoration in control dogs. Heart rate, cardiac output, aortic pressure, dP/dt, and left ventricular size were normalized by retroperfusion. Hemodynamics remained depressed in controls. Following reperfusion, 10 of 13 treated dogs recovered while only 2 of 13 untreated dogs survived. Gundry considered diastolic retroperfusion a potentially useful support in acute myocardial ischemia prior to emergency coronary artery bypass, Farcot (37) compared synchronized retroperfusion vs. reperfusion, instituted at 10 min during a 180 min coronary occlusion in dogs. 170 min of diastolic retroperfusion increased transmural blood flow in the ischemic zone to 47% of its preischemic value, with favorable redistribution towards endocardium, and simultaneously significantly reduced the extent of regional dysfunction. These improvements were intermediate compared with an equivalent early antegrade reperfusion.
There followed in the early 1980s a series of concepts of enhanced retroperfusion. Thus, Lang and Meerbaum (unpublished) examined a combination of retroperfusion with intraaortic balloon pump cardiac unloading. Feasibility and some benefits were noted, but the system was complex. Meerbaum (79) investigated a moderately hypothermic form of synchronized retroperfusion in closed chest dogs with 3 and 6 h LAD occlusion, treated from 30 min occlusion on. Arterial blood was cooled down at the pump and then deliv-

ered retrogradely in diastole to acutely ischemic myocardium, whose regional temperature decreased by a few degrees C. Heart rate was reduced by about 30 beats/min, and rate-pressure product and systemic vascular resistance decreased significantly. Limited data indicated that the observed infarct size reduction exceeded that achieved by normothermic retroperfusion. Two-dimensional echo quantitation revealed reversal of ischemic region dysfunction and also significant enhancement of function in adjacent and remote zones of the heart. Haendchen (54) applied great cardiac vein hypothermic retroperfusion for 2½ h in dogs during a 3 h LAD occlusion, followed by 7 days' reperfusion. Control dogs were equivalent but without retroperfusion treatment. Evidence was presented that retroperfusion resulted in significant improvements in post-reperfusion cardiac function recovery, along with substantial infarct salvage. Haendchen demonstrated with two-dimensional echocardiography that early reperfusion edema could be avoided by the retroperfusion.

Povzhitkov combined retroperfusion with retrograde coronary venous infusion of PGE_1 (94a) or Manitol (94b). He showed during proximal LAD occlusion that PGE_1-enhanced retroperfusion improved function even in the apical region of the left ventricle where acute ischemic injury is frequently difficult to reverse. Significant infarct salvage was demonstrated. Selective use of cardioactive drugs in the retrograde perfusion thus appeared to be a potentially worthwhile approach. Kordenat (70) tried retroperfusion of ischemic myocardium with methysergide and dipyridamole in a dog model with thrombotic LAD occlusion. 30 min after angiographically confirmed LAD occlusion, the drug was infused as a single bolus into the great cardiac vein through a balloon catheter. In a control occlusion group, stroke volume and cardiac output decreased and total peripheral resistance increased. Drug retroinfusion prevented these derangements and provided improvements, evidencing protective effects during evolving infarction. Berdeaux (17, 18) reported on failure of supplemental verapamil or nitroglycerin infusion to potentiate the synchronized retroperfusion benefits during acute ischemia. In open chest dogs with 180 min proximal LAD occlusion, treatment was started 10 min post occlusion and maintained for 170 min. The retroperfusion-induced increase in regional myocardial blood flow was further enhanced, but the endocardial-to-epicardial flow ratio decreased through a major increase in the subepicardial flow. Ischemic zone functional recovery actually deteriorated, especially with verapamil.

Two further extensions were reported recently. In one, Meerbaum (80) used synchronized retroperfusion in closed chest dogs with experimental thrombotic LAD coronary artery occlusion. Based on prior observations which suggested that up to 25% of the retroinfusate might under conditions of severe ischemia be delivered from the regional coronary vein into the corresponding occluded coronary artery, limited studies were performed with intravenous vs. coronary venous retroinfusion of streptokinase, in a dosage of 2000 IU/min corresponding to coronary artery thrombolytic infusions. The LAD thrombus was lysed in each of the dogs, but much later in the intravenous group compared to intermittently or continuously retroinfused dogs. Reperfusion became apparent in about 23 min and was fully established within about 50 min from retrograde streptokinase injections, initiated after 1 h or more of LAD obstruction. Reperfusion arrhythmias were not encountered. Echo observations suggested relatively rapid return of ischemic zone function early post reperfusion. Based on the limited study, Meerbaum pointed out that thrombolytic retroperfusion may provide essential circulatory support pending achievement of satisfactory reperfusion, in addition to delivering the lytic agent into the occluded

artery for retrograde dissolution of the clot. In a different recent application, Karagueuzian (65) retroinfused procaine amide into the great cardiac vein in dogs with 3–12 days' LAD occlusion and demonstrated that such retrograde treatment can, most of the time, terminate induced sustained ventricular tachyarrhythmias (in 69% of cases). Intravenous procaine amide treatment proved effective in only 11% of the tachycardia episodes, the remainder being refractory. By measuring myocardial tissue content, it was shown that the antiarrhythmic drug was selectively delivered into the infarcted zone, yielding a ten fold concentration compared to the remote noninfarcted region. Otsu (89) checked in an analogous manner myocardial concentrations and antiarrhythmic effects of lidocaine administered via the coronary veins. Retrograde administration during coronary vein balloon occlusion was most effective in interrupting ventricular tachycardia. The clinical potentials of such a retroperfusion application may be considerable.

Recently, Ksiezycka (71) and Zalewski (125) performed useful comparative studies of various regional retroperfusion methods. When the LAD was occluded for 6 hours and the adjacent anterior interventricular coronary vein retroperfused between 10 min and 6 h, infarction (as % of the risk area) was significantly reduced from 89.4 to 39.8% of the left ventricle, compared to untreated controls. Zalewski studied 73 open chest dogs in 7 groups: 1) control occlusion; 2) 60 ml/min veno-coronary vein shunt; 3) a low flow arterial-coronary vein shunt; 4) 60 ml/min arterial-coronary vein shunt; 5) 60 ml/min arterial shunt to the great cardiac vein; 6) diastolic occlusion of great cardiac vein during 60 ml/min arterial blood retroperfusion; 7) intermittent pressure controlled occlusion of great cardiac vein without arterialization. Infarct size in these groups was 100%, 86%, 63%, 54%, and 85%, respectively. The important conclusion was that neither veno-venous nor simple intermittent occlusion significantly reduced infarct size, whereas the remaining arterial blood retroperfusion techniques reduced infarct by 34–46%[1]). Myocardial hemorrhages were encountered in some instances when high flow retroperfusion was apparently associated with insufficient coronary venous drainage.

With normothermic synchronized retroperfusion of arterial blood approaching clinical application, attention turned to safety, logistics and promptness of this treatment's efficacy. Two studies in closed chest dogs with 6 h LAD occlusion addressed these issues. Yamazaki (123) again demonstrated hemodynamic benefits, significant improvement of regional and global function and substantially decreased infarct size, using synchronized retroperfusion from 30 min to 6 h LAD occlusion. In addition, Yamazaki turned retroperfusion off for 5 min at 1 h post occlusion, which resulted in reversal of the benefits; when retroperfusion was turned on again, all indices of cardiac performance promptly returned. In a corresponding safety study, Drury (30) found that synchronized retroperfusion caused no vascular damage, no edema and no red cell hemolysis or platelet destruction. He concluded that the methodology appears ready for clinical applications. Initial clinical trials have begun, and – so far – include synchronized retroperfusion support during percutaneous transluminal angioplasty and treatment supporting myocardial viability in patients with unstable angina awaiting bypass surgery. Human coronary venous catheterization experience is being accumulated using the special retroperfusion catheters; it appears that catheter placement can be achieved within minutes, and full mobilization of the retroperfusion system should be feasible within 15–20 min.

Comment: Clinically oriented retroperfusion methods have the potential to promptly

[1] See also Mohl W., PICSO status report 1985; this volume, p. 68

provide for a few minutes or a few hours and up to several days a retrograde circulatory support delivering oxygen, substrates and pharmacologic treatment to jeopardized ischemic myocardium. There is the supplementary potential of retrograde delivery of thrombolytic and antiarrhythmic agents. Retrograde measurements and contrasts can be applied to study the heart's performance and delineate underperfused myocardium. Yet, there remain questions to be answered and improvements to be made in the systems. Thus, excessive pressure and flow in the coronary veins can be hazardous. Conversely, excessive shunting can severely compromise retroperfusion effectiveness. Retroperfusion systems may require flexibility to adjust intravascular pressures and flows, and account for altered heart rate. Microcirculatory mechanisms during retroperfusion remain ill defined (91), and biochemical or myocardial metabolic data are scarce. Clinical evidence is rather limited, so that the extensive data from animal experiments cannot as yet be placed in appropriate perspective.

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Synchronized coronary sinus retroperfusion current clinical perspective

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The concept of retroperfusion of the heart via the coronary sinus resulted from the realization that the coronary venous system is not affected by the atherosclerotic process. F. H. Pratt in 1898 demonstrated that the heart could be maintained for some time by the retrograde flow of oxygenated blood via the coronary sinus (18). Pratt perfused the coronary sinus of a freshly extirpated cat heart with defibrinated arterialized blood and was able to maintain regular coordinated contractions for one and one-half hours. In 1948, Claude Beck showed that the shunting of arterialized blood to the coronary venous system could relieve angina in the presence of chronic coronary artery disease (1, 2). The Beck procedure utilized the placement of a free vein graft between the aorta and the coronary sinus, followed by the subsequent partial ligation of the coronary sinus immediately proximal to its entrance into the right atrium. This second stage of the procedure was aimed at preventing the complete egress of blood into the right atrium thus forcing a portion of the aortic blood retrograde into the venous tree. Beck's work predated coronary artery bypass graft (CABG) surgery and was replaced by that procedure because it directly re-established blood flow to the myocardium.

In 1956, Lillehei described the maintenance of the circulation by an extracorporeal perfusion system in a patient with aortic stenosis (13). Standard cardiopulmonary bypass was combined with the use of retrograde perfusion of oxygenated blood through the coronary venous system to maintain myocardial viability.

Meerbaum and colleagues in 1976, developed the procedure known as synchronized coronary venous retroperfusion (14). This technique differs from the Beck procedure and other surgical coronary venous retroperfusion techniques in several ways. First, appropriate synchronization provides retroperfusion only during diastole, while permitting normal physiologic coronary venous drainage during systole. Second, the method is intended as a temporary treatment for acute myocardial ischemia. There are several studies in both dogs and baboons that have shown the effectiveness of this intervention in the reduction of infarct size after acute coronary occlusion (5–8, 11, 19, 21).

Menasche in 1982, during aortic valve surgery, delivered cardioplegic solution retrograde into the coronary sinus (16). This was performed with a balloon-tipped catheter inserted into the coronary sinus through the right atrium. They found retrograde coronary sinus perfusion to be a simple, safe and effective means of cardioplegic protection during aortic valve surgery (Table 1).

The beneficial effects of synchronized coronary sinus retroperfusion (SCSR) in experimental animals have been well documented. A recent study demonstrated the extent of myocardial infarction expressed as a percentage of the zone at risk evolving to necrosis was significantly reduced by various types of arterialization of the cardiac venous system

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Table 1. Historical perspective.

1898 F.H. Pratt	Beneficial effect of arterialization of cardiac venous system
1948 C.S. Beck	Surgical revascuclarization in patients with coronary artery disease by arterialization of the coronary sinus
1956 C.W. Lillehei	Retrograde coronary sinus perfusion during aortic cross-clamping for visualization of the aortic valve
1976 S. Meerbaum and E. Corday	Selective retroperfusion as a catheterization procedure to reduce myocardial damage after ischemia
1982 P. Menasche	Retrograde coronary sinus perfusion of cardioplegia
1985 University of Massachusetts Medical School	Retroperfusion in humans with unstable Angina
1985 J.C. Farcot	Retroperfusion in humans during angioplasty

(21). An alternate coronary sinus intervention, pressure controlled intermittent coronary sinus occlusion (PICSO) of the great cardiac vein did not significantly reduce the infarct hypoperfused zone ratio and therefore did not appear to salvage ischemic myocardium[1]). Not surprisingly, retroperfusion with venous blood did not result in myocardial protection either. These investigators also found that deleterious effects of retroperfusion, such as intramyocardial hemorrhage, are uncommon with arterialization of the cardiac veins, except when perfusion of a local cardiac vein with high flow occurred.

In animals, the microsphere technique has been used to demonstrate the distribution of regional myocardial blood flow (RMBF) in ischemic and nonischemic myocardial segments during diastolic synchronized retroperfusion of acutely ischemic myocardium (3). Retroperfusion is effective in the treatment of acute myocardial ischemia by increasing RMBF of the ischemic zone to approximately 50% of the control (non-occluded) flow with redistribution of this flow towards the endocardium. That retroperfusion particularly benefits the endocardium is of importance since the endocardium is the most sensitive to ischemia. Myocardial tissue samples demonstrate the presence of microspheres within coronary veins after the injection through the retroperfusion catheter and within the distal portion of arterial branches of the ligated coronary artery.

The coronary sinus is the blood conduit in the continuation of the great cardiac vein and empties into the right atrium. It has a length of 20–65 mm, its diameter in the midportion is 6–16 mm, and is positioned superficially in the ventricular sulcus. The current SCSR technique employed is synchronized delivery of arterialized blood, using an auto-inflatable occlusive balloon catheter placed in the coronary sinus. Retrograde delivery through the coronary venous system occurs during cardiac diastole by synchronization to the ECG. Physiologic coronary venous drainage occurs with deflation of the balloon, during cardiac systole.

Based on the work done in our laboratory at the University of Massachusetts Medical School (8, 9), along with other institutions (5, 21), and in addition to refinements in equipment and the documentation of safety (5) of SCSR in animals, studies to evaluate the feasibility and safety of this intervention in humans have been initiated.

The retroperfusion system currently being used was developed by USCI (Division of CR Bard Inc, Billerica, MA). This system consists of a piston driven pump, pump console and extracorpeal circuit (Table 2). A physiologic monitor is also included with the system

[1]) See also Mohl W., POCSO status report 1985; this volume, p 68

Table 2. Retroperfusion system.

1. *Arterial supply catheter* – to shunt arterial blood to pump
2. *Pump chamber assembly* – piston driven chamber propels blood into coronary sinus by mechanical displacement
3. *Monitor console* – permits ECG synchronization of blood delivery and regulation of the amount of flow
4. *Coronary sinus catheter with autoinflatable balloon* – permits intermittent occlusion of the coronary sinus to allow retrograde flow without needing a separate inflation vehicle (gas)

which permits the synchronization of blood delivery. There are controls which regulate the amount of retroperfused blood flow and the period of time during the cardiac cycle when retroperfusion can occur. Coronary sinus augmented flow can be given with each cardiac cycle or at preset ratios (i.e. 1 : 1, 1 : 2 or 1 : 3). The pump chamber and tubing are disposable.

Arterial blood is obtained through a catheter inserted percutaneously into the femoral artery. This catheter is connected to the inlet tubing of the pump assembly. The coronary sinus catheter is placed via any central venous access site and advanced to the coronary sinus. The coronary sinus catheter has an end hole through which arterial blood is delivered. There is an auto-inflatable balloon located just proximal to the tip of the catheter. The outlet tubing of the pump is connected to the coronary sinus catheter thus completing the circuit.

The correct position of the catheter is determined by radiographic examination. The patient receives a bolus of heparin and is then maintained on a continuous infusion throughout the duration of retroperfusion. Retroperfusion is instituted with incremental increases in flow rates until relief of symptoms is achieved or until the maximum output of the machine (150 cc/min) is reached. Continuous hemodynamic monitoring is performed in all patients in addition to frequent assessment of hematologic parameters for the assessment of safety. Comparison of clinical parameters prior to therapy was made against the same clinical parameters while on retroperfusion. The intervention is maintained until definitive mechanical therapy (angioplasty or coronary artery bypass surgery, if suitable coronary anatomy exists) is performed. All patients underwent cardiac catheterization to delineate their coronary anatomy.

Our clinical experience to date has focused on patients with unstable angina (10) and those undergoing coronary angioplasty (17) (Table 3). In patients with unstable anterior ischemic signs and symptoms, SCSR was found to be a feasible bedside technique. Using

Table 3. Clinical experience.

Unstable angina	PTCA
Anterior ischemia	LAD disease
Feasible, bedside technique	Feasible cath. lab. procedure
Safe for periods up to 50 hours	Safe, requires 2 extra lines
Effective in relieving pain, ECG changes and drug requirement	Effective in prolonging inflation times, decreasing symptoms and lengthening time to ECG changes

fluoroscopy, retroperfusion can be instituted within a short period of time and is no more complicated than performing any fluoroscopically guided right heart catheterization. Patients have tolerated the institution of retroperfusion extremely well with rapid relief of symptoms. The intervention has been employed for periods in excess of 2 days. It has proven to be extremely effective in relieving anginal symptoms, ischemic ECG changes and decreasing the need for pain medications. Examination of the heart in selected cases has revealed no evidence of surface or coronary venous damage. The effects of retroperfusion on hematologic parameters is that which would be expected from carefully controlled animal studies. That is, a slight decrease in hematocrit, hemoglobin and platelet count along with a slight elevation in plasma free hemoglobin. None of these changes are clinically significant. Hand injection of radiographic contrast material into the blood entering the coronary sinus has revealed widespread perfusion of the arterialized blood. Cineangiography of these injections has raised the possibility that the retrogradely delivered contrast was reaching the coronary arteries as evidenced by filling of vessels that appear to have luminal irregularities consistent with an atherosclerotic artery.

In patients undergoing angioplasty for left anterior descending coronary artery disease, synchronized coronary sinus retroperfusion has also been evaluated. SCSR is a safe and feasible procedure when performed in the cardiac catheterization laboratory. It requires the placement of two additional catheters; one in the femoral artery and the other in a vein for placement of a catheter into the coronary sinus. Preliminary studies have shown that SCSR allows for prolonged inflation times of the angioplasty balloon, decreases ischemic symptoms and lengthens the time from balloon inflation to ECG changes.

In the near future SCSR will hopefully move from a research tool to a widely accepted and utilized modality for the treatment of patients with a variety of cardiac abnormalities. The syndrome of unstable angina has provided the opportunity to study the feasibility and safety of retroperfusion while at the same time providing preliminary information on the efficacy of this intervention in humans.

Over the past several years we have accumulated extensive experience in the treatment of patients presenting with unstable angina, acute myocardial infarction and post-infarction angina. Advances in medical and surgical therapies have changed the physician's approach to myocardial ischemia.

Unstable angina pectoris is an alarming clinical syndrome with an accelerating pattern of ischemic chest pain, variably leading to myocardial infarction and death. Myocardial ischemia results from an imbalance in the oxygen supply-demand relationship. Two major factors influencing myocardial oxygen supply are 1) alterations of the coronary arteries and 2) the general cardiovascular status of the patient.

Coronary arteriography has revealed multivessel coronary disease in the majority of patients presenting with the syndrome of unstable angina. Clinical instability and infarction may be the result of episodic reductions in myocardial oxygen supply due to large artery spasm or platelet aggregation at or near a partially occlusive atherosclerotic plaque.

The efforts to preserve viable myocardium have been aimed at improving this imbalance between myocardial oxygen supply and demand. Until recently, most of these efforts have been directed at reducing demand through pharmacological techniques. The results have not been impressive and focus has now shifted to the re-establishment or improvement of arterial blood supply. Preliminary results are encouraging.

Reperfusion may come about through several routes; spontaneous thrombolysis, thrombolytic agents such as streptokinase, urokinase and tissue plasminogen activator; percu-

taneous transluminal coronary angioplasty (PTCA); and/or coronary artery bypass graft surgery (CABG). The more rapid the reestablishment of adequate blood flow, the more likely the salvage of the jeopardized myocardium. To date, the vast majority of interventions have been directly on the coronary arterial system.

Synchronized coronary sinus retroperfusion is a potential means of maintaining myocardial viability utilizing a relatively fast and safe intervention which requires only a simple catheterization procedure. By preserving myocardial oxygen supply with this indirect method, time will be gained during which the most appropriate means of direct reestablishment of blood flow can be chosen.

Preliminary human experience with SCSR indicates that it can be instituted promptly and without any significant risk to the patient. It appears that this technique improves ischemia induced dysfunction in the distribution of the LAD and can be used as a method to support the myocardium pending definitive therapy. The early human experience with retroperfusion is very encouraging and will serve as an impetus for expanded clinical trials.

There are numerous potential clinical applications of SCSR that might be evaluated in the future (Table 4). In addition to utilizing this intervention in patients with unstable angina and during PTCA, it should, based on animal data, prove to be very effective in the management of patients with acute myocardial infarction. It would support the myocardium during evolving infarction and allow time for more definitive therapy to be employed. More definitive therapy may take the form of drug administration such as thrombolytic agents (15), vasodilators (4) or calcium channel blockers directly into the coronary sinus. Retroperfusion may also prove extremely valuable in treating patients who are electrically unstable and require antiarrhythmic drug treatment (12). Giving antiarrhythmic medications directly to the myocardium where it is needed via the coronary sinus may prove to be an extremely important development in the management of refractory arrhythmias and in the acute assessment of drug therapy.

There are ample data to suggest that the retroinfusion of cold cardioplegia during bypass surgery is a viable option in selected cardiac surgical procedures, including patients with aortic valve disease and left main coronary artery disease. By continuously delivering cardioplegia to the myocardial area at greatest risk (that area beyond critical narrowings), better protection of ischemic myocardium may be achieved (17). This system would not interfere with the surgical procedure and could be performed concomitantly. Retroperfusion may also assist in patients requiring surgery for aortic dissection, acute mechanical cardiac complications and during non-cardiac surgery in patients with known coronary

Table 4. Potential application of retroperfusion.

Unstable angina	Support and stabilization of ischemic myocardium
Coronary angioplasty	Allow longer inflation and attempts of more difficult cases including left main stenosis, support of patients should complications occur
Myocardial infarction	Limit infarct size
Cardioplegia	Continuous retrograde delivery; especially for patients with aortic stenosis and left main disease
Drug delivery	Fibrinolytic agents, vasodilators, anti-arrhythmics
Support of cardiac patients during non-cardiac surgery.	

artery disease. Finally, it may be that this technique will aid in the differentiation of ischemic from fixed mechanical mitral regurgitation as assessed at the time of cardiac catheterization.

The clinical future of retroperfusion looks extremely bright. With anticipated advances in the development of improved equipment, the procedure will become simpler and the indications for its use will increase. The true effectiveness of retroperfusion awaits the results of clinical trials. However, retroperfusion is no longer limited to the animal laboratory, the era of human evaluation has arrived. The pioneering work of Beck, Corday, Meerbaum and others has now become a clinical reality.

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PICSO status report 1985

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Pressure controlled intermittent coronary sinus occlusion (PICSO), which has been evaluated in several experimental series, is currently undergoing various explorative clinical studies. It is therefore necessary to reassess all the information and findings that have so far been gathered with respect to this new intervention. While it appears relatively simple to evaluate the efficacy of an intervention in an experimental setting, we are just now in the process of learning how we are to proceed in the evaluation of its clinical significance. In this attempt we feel the need of an enhanced exchange of experimental data and an even more extensive evaluation of the pathomechanisms involved, as well as of further refinement of the technology on which PICSO essentially relies. But at the same time we feel it to be a legitimate approach of ours to test the effect of PICSO in humans (8) so as to make it available for clinical use in routine settings to the benefit of the patient.

Basic principles of PICSO

Pressure controlled intermittent coronary sinus occlusion is an alternative method for the delivery of flow towards an ischemic area.
During the temporary blockade of the coronary sinus a redistribution of venous flow and plasma dense fluid causes more extensive flow into underperfused zones. This happens in accordance with the rise and fall of certain pressure gradients in the microcirculatory bed (11) (*redistribution phase*). A second beneficial effect is being produced by the subjection of ischemic myocardium to the reactive forces of buffer systems and the action of osmotic, ionic and mechanical forces (*equilibrium phase*). As the coronary sinus pressure gradually increases until a certain plateau of systolic pressure peaks and thus pressure control has been reached (hence the name pressure controlled intermittent CSO), redistribution and subsequent equilibrium of inflowing venous blood and ischemic metabolites are established (Fig. 1).

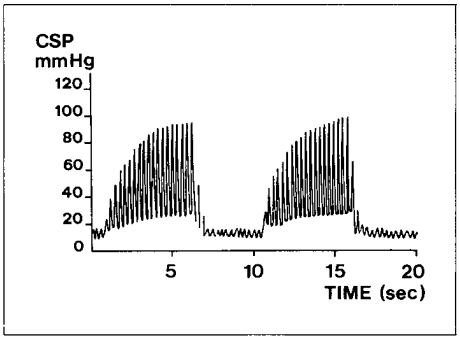

Fig. 1. Coronary sinus pressure under PICSO.

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During the intermittent release of CS blockade a rapid change in outflow resistance allows for sufficient drainage. During this rapid venous drainage, toxic waste that has been accumulated in the course of progressive ischemia is being washed out (*washout phase*). This phase is followed by a hyperemic response in coronary artery flow (6).
This cycling of high flow and low pressure (*intermittent coronary sinus release*) and the periodic changes to high pressure (*CS occlusion*) in the venous vasculature associated with low flow appear to reverse the ischemic processes and to bring them to a halt. We thus hypothesize that these mechanisms will ultimately prevent cell death and enhance recovery during reperfusion, as seen in experimental series.

Experimental PICSO series

Table 1 reviews the PICSO literature currently available. Reduction of infarct size as found by Mohl et al. has been the subject of interest of four research groups other than the PICSO team in Vienna. While two of them produced evidence which confirmed the beneficial effect of PICSO, the other two failed to produce favourable results. And with due reason these latter results have met with rather severe criticism on our part; in none of the studies was PICSO applied properly. It appears that the main reason for the failure to bring about positive results must have been the absence of continuous monitoring of the coronary sinus pressure. Apparently, Diltz's deviation from normal timing (she used 30 s of occlusion and 30 s of release) and her subsequent failure to fully achieve pressure control must have been the reason for her negative findings (1–3, 5, 9, 13). As to the second negative study we strongly suspect that, had Zalewski kept to the usual procedure of continuous monitoring, his results would have been of a totally different nature. Many years of experience with this intervention, especially with improper approaches as to the technology involved, have taught us that PICSO fails to be a reliable mechanism unless CS pressure dynamics are monitored on line and unless any changes in catheter position or heart performance are immediately responded to through an instant repositioning or readjustment of cycle length.
At present, findings on the effects of PICSO on ischemic dysfunction are only available from our group. So far, experimental results have found PICSO to distinctly improve ischemic dysfunction, both during coronary artery stenosis and during coronary artery occlusion. One series showed significant improvement achieved through adjustments of

Table 1. PICSO literature

1. Mohl	(6)	1984	Development and rationale of PICSO
2. Mohl	(9)	1984	PICSO reduction of infarct size
3. Ciuffo	(1)	1984	ICSO reduction of infarct size
4. Mohl	(10)	1985	PICSO improvement of ischemic function
5. Jacobs	(5)	1985	PICSO reduction of infarct size
6. Zalewski	(13)	1985	ICSO no reduction of infarct size
7. Diltz	(2)	1985	PICSO no improvement of dysfunction, no reduction of infarct size
8. Guerci	(3)	1985	PICSO reduction of infarct size

cycle length (4, 10, 12). All in all the pathomechanism and mode of action of PICSO appear to be washout and redistribution of flow to ischemic areas, as reported by our group and corroborated by Ciuffo (1, 11).

Challenge of future research (ICSO vs. PICSO)

The state-of-the-art of PICSO interventions facilitates the preservation of myocardial function, metabolism and ultrastructure and an extension of the period of reversible cell injury. However, we are aware of the fact that the present knowledge on the interactions between pump cycles and coronary venous pathophysiology needs to be enhanced by further research stimuli and that the technology involved still needs more sophisticated adaptation and modification so as to meet the requirements of an application in humans. Some of the investigations which failed to produce evidence of the beneficial effects induced by PICSO have been found to have taken advantage of a trade-off between the rigid regimen of CS occlusion/release cycles (ICSO) and the CSP dynamics of PICSO. Under these circumstances we must not be surprised that the respective intervention had no or merely a slight beneficial effect.

Recently, we have been focusing much of our own research endeavours on this specific problem; according to our own findings significant individual changes in coronary sinus pressure and dynamics occur within one and the same rigid regimen of occlusion/release times. Since ICSO does not adapt to these changes, CS occlusion, as of necessity, fails to produce its beneficial effects or even risks becoming counterproductive. This is due to the fact that an inadequate duration of coronary sinus release appears to be bound to lead to insufficient drainage and hence, to bring about edema formation and a decrease in coronary artery inflow rather than washout and hyperemic response. Figure 2 shows the variations in impact on the 90% plateau level due to different occlusion and release times. Note the differences in the slopes of the coronary sinus pressure in the two groups presented. Occlusion and release do not only depend on the coronary venous capacitance but also on heart rate and coronary venous flow. Therefore, a rigid coronary sinus occlusion-/release regimen will never have an optimum effect since, by its nature, it cannot adapt to the various parameters which come into play. While an extension of coronary sinus pressure elevation beyond the point where the 90% plateau level is reached and a coronary sinus release time of less than 3 s produce insufficient venous drainage and can be counter-

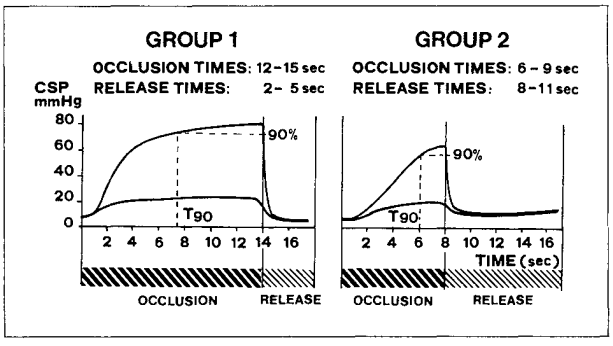

Fig. 2. Varying impact on 90% plateau level due to differences in occlusion and release times between groups.

productive to arterial flow, a coronary sinus occlusion shorter than that for 90% plateau levels and an unnecessary extension of coronary sinus release beyond the time needed for sufficient venous drainage have been found to produce no effect.

Strategic approach to PICSO clinicals

PICSO has been specifically designed to meet the requirements of treatment of acutely jeopardized myocardium. Ethical considerations and questions as to its feasibility have so far limited the application of this new intervention to explorative selective settings. We have therefore taken to a different approach, i.e. to evaluate PICSO in selective intraoperative randomized trials during reperfusion following global ischemia. This explorative study is assumed to eventually answer the remaining questions as to its safety and feasibility and to give some indication as to its effectiveness in the prevention of reperfusion injury after global ischemia. At this point we are quite confident that after completion of this study we will be able to take the method one step further and apply our present study protocol in perioperative settings, with the ultimate aim of laying down specific criteria for the selection of a surgical subpopulation of patients who are liable to actually benefit from PICSO. We suggest that by then study programmes be launched in catheter labs that are to run parallel to our own program, so as to determine the efficacy of PICSO on global ejection fraction and cardiac metabolism in pacing-induced ischemia. The clinical significance of PICSO will not, however, be fully established, and will remain a challenge, until we have succeeded in establishing the safety of PICSO beyond any doubt, so that then we have actually started application in humans with acute myocardial infarction.

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Retrograde cardioplegia: myocardial protection via the coronary veins – 1986

S. R. Gundry

Introduction

Although the concept of providing nourishment to the heart via the coronary venous system has been described since the late 19th century and flourished briefly as a clinical method of providing temporary relief of myocardial ischemia during the 1950s and 1960s, the technique of utilising the coronary veins to deliver myocardial protective agents and/or cardioplegia never gained much widespread acceptance until the past few years. Although improvements were rapidly made in the constitution of cardioplegic solutions during the past ten years, concurrent with the burgeoning popularity of coronary artery revascularisation, one of the principal limitations in myocardial protection remains the non-uniform distribution of cardioplegic solutions distal to coronary artery occlusions or stenoses. Moreover, disappointment with the cumbersome and occasionally dangerous methods of direct coronary ostial perfusion during aortic valve replacement has led to a resurgence of interest into alternative forms of myocardial protection, including use of the coronary veins/sinus to deliver cardioplegia in a retrograde fashion into the heart.

It is the purpose of this chapter to provide a brief overview of the past developments in utilising the coronary venous circulation to provide myocardial protection during cardiopulmonary bypass and to update the reader on the current status of coronary venous retroinfusion of cardioplegic agents in 1986.

The reader is referred to the preceding chapters on the anatomy of the coronary venous circulation elsewhere in this volume in order to familiarise themselves with the anatomic basis for using the coronary veins as a method of delivering protective agents.

It appears to be Pratt in 1897 (23) who, in a series of elegant experiments, noted that an isolated heart could be made to beat vigorously for several hours in a non working state by perfusion of only the left ventricular cavity and hence the myocardium via the Thebesian veins. Additional experiments using the coronary sinus for inflow of warm fresh blood confirmed that the heart could be kept beating indefinitely using only the coronary veins. In 1943 Roberts (24, 25) demonstrated similar findings using blue dye injections to demonstrate complete filling of the capillary network of the heart via the coronary sinus. These advances, coupled with Beck's experiments which are delineated elsewhere in this book, led several groups, working simultaneously, to attempt myocardial protection during initial open-heart procedures, using the coronary sinus. Blanco (1) in 1955 reported that in dog hearts, a combination of cross circulation and perfusion of the coronary sinus at 50 mm Hg pressure could allow direct visualisation of the aortic valve while maintaining normal myocardial function and sinus rhythm for 5–7 minutes' duration.

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Shortly thereafter Lillehei (17) and his colleagues from the University of Minnesota reported their success with correction of calcific aortic stenosis in man by means of a pump oxygenator coupled with retrograde coronary sinus perfusion with oxygenated blood flowing at 125 cc/min. At normothermia, the heart was perfused in a retrograde fashion for 11 minutes and they reported that the heart remained beating and clearly took up oxygen.

Subsequent success was reported by Gott (6) in 1957. Seven patients survived aortic valve surgery using retrograde perfusion of the coronary sinus during aortic cross-clamping. Gott noted that the human venous anatomy appeared much more suitable than the dog's anatomy for perfusion of both ventricles; he observed that more of the right ventricle was subtended by the coronary sinus. While one third of all human hearts that he examined had a drainage pattern similar to that of the dog, one third of hearts demonstrated almost complete drainage of the right ventricular coronary blood into the coronary sinus while in another third, a lesser proportion of the right ventricular myocardium was drained by the coronary sinus. Lastly, Gott further noted that when pressures exceeded 50 mm Hg within the coronary veins, myocardial contractility appeared depressed, while a mean pressure of 30 mm Hg appeared to be the optimal pressure for perfusing the veins.

Despite this initial success with perfusion of the coronary sinus with oxygenated blood, the advances in antegrade myocardial protection using cardioplegic agents in the late 1950s soon completely overshadowed any benefits that protection of the heart via the coronary sinus might have had. Indeed, in 1958 Shumway (27) categorised the pros and cons of retrograde versus antegrade coronary perfusion and noted at that time that the 3 main problems with the retrograde technique were potential heart block from suturing in catheters around the coronary sinus, unusual myocardial contractility during retrograde perfusion and lastly, diminished right coronary artery retrograde flow which he observed in clinical cases. His conclusions, and those shared by many, even at the present time, were that direct coronary ostial injection of blood and/or cardioplegic solutions was the most preferable method of delivery for myocardial protection (Table 1).

Despite this apparent set-back, interest in utilising the coronary veins as a method of myocardial protection continued, with a new focus on protecting areas of the heart which

Table 1. A comparison of advantages and disadvantages of cardioplegic techniques.

	Pros	Cons
Antegrade cardioplegia	1) Ease of administration 2) Existing catheter design 3) Rapid administration	1) Inadequate distribution 2) Coronary ostial injury
Coronary sinus cardioplegia	1) Uniform distribution 2) No cannulae near aortic valve 3) No damage to coronary ostia 4) Slow, even cooling	1) May need atriotomy 2) Slow administration 3) Damage to coronary sinus or conduction system 4) ?Protection/perfusion right ventricle
Right atrial cardioplegia	1) Ease of administration 2) Slow, even cooling 3) No damage to conduction system or coronary sinus	1) Right ventricular distension 2) Uneven cooling of right ventricle 3) Slow administration

potentially might receive inadequate blood flow owing to coronary arterial stenoses or occlusions (5, 15). In 1957, Davies and his colleagues from the Massachusetts General Hospital reported their experimental study in which dogs with left main coronary artery occlusions were given retrograde perfusion of the coronary sinus with oxygenated blood during artic cross-clamping. Following relief of their left main occlusion, all dogs treated in the above manner survived. In contrast, dogs which were not treated with coronary sinus retroperfusion during the bypass period could not be weaned from bypass. It is of interest that in this model the aorta was cross-clamped and no egress of blood was allowed through the coronary ostias. These investigators felt that if egress through the coronary ostia were prevented, blood would be forced back through the capillary beds and into other areas of the heart less well served by the coronary sinus-venous connections, hence perfusing more of the myocardium.

In 1973, Lolley and his colleagues reported that retroperfusion of the heart with a solution of glucose, insulin and potassium during a period of 30 minutes of anoxic arrest could preserve myocardial function. They noted that the effluent ratio from the right ventricle versus the coronary artery ostia was 3 : 1 suggesting that although capillary perfusion took place, a great deal of the cardioplegic solution traversed the heart via sinusoidal and Thebesian routes. They further demonstrated that the heart took up glucose that was present within the solution.

In 1975 Poirier (22) and his colleagues from the National Institutes of Health reported that retrograde coronary sinus perfusion could protect hearts for at least one hour at either 37 or 29 °C. They noted that full functional recovery was obtained in hearts protected in such a manner at 29 °C although poor right ventricular function was present in those hearts preserved at normothermia.

In 1978, Chiu (28) and his co-workers showed that retrograde coronary sinus perfusion could provide efficient core cooling of the myocardium in the presence of complete coronary artery occlusion. They showed minimal tissue oedema and good preservation of glycogen stores in experimental hearts receiving retrograde coronary sinus cardioplegia.

During the late 1970s and early 1980s, several groups working independently (5, 15) noted that myocardial protection was inadequate distal to coronary artery occlusions or stenoses both experimentally and clinically, owing to poor perfusion of the myocardium with antegrade cardioplegic solutions. Encouraged by previous work utilising diastolic retroperfusion of the working heart, our group showed in 1982 (7, 8) that coronary sinus blood cardioplegia provided better protection of the myocardium distal to coronary artery occlusions than similar antegrade delivery. Shortly thereafter Menasche (20) reported on the full recovery of left ventricular function in patients undergoing aortic valve replacement utilising retrograde coronary sinus cardioplegia, while Gardner and his colleagues (2) showed that continuous retrograde coronary sinus infusion of cardioplegic solutions could also provide excellent myocardial protection. Using instrumented dogs, Hashem in 1984 confirmed Menasche's observation that retrograde cardioplegia provided equal ventricular functional recovery to that obtained with coronary ostial cardioplegia.

Recent developments

While it was becoming rapidly clear that retrograde coronary sinus cardioplegia could provide excellent protection of the myocardium distal to coronary artery occlusions some

question remained as to whether these same effects occurred in hearts with coronary artery stenoses. Recently elegant clinical experimentation (21, 26) using thermography has demonstrated much better and more rapid cooling of myocardium served by occluded or stenosed coronary arteries using retrograde cardioplegia.

Recent investigation by our group has additionally shown in experimental animals that myocardial protection distal to coronary artery stenoses as well as occlusions is improved with retrograde blood cardioplegia (10). Moreover we have been able to show that the diastolic compliance of the ventricle appears to be improved compared to antegrade cardioplegic methods (11).

Owing to the often inadequate drainage of right ventricular veins into the coronary sinus, protection of the right ventricle with coronary sinus cardioplegia theoretically may be inadequate. In an effort to eliminate this inadequate protection of a portion of the myocardium, Fabiani and Carpentier developed a technique called right atrial cardioplegia. Cardioplegia is infused directly into the right atrium, combined with the occlusion of both venae cavae and the pulmonary artery. By pressurising the right atrium to 50 mm Hg, the same pressure is then transferred into the right ventricle and coronary sinus, thereby hopefully providing flow through the Thebesian venous system of the right ventricle as well as the coronary sinus. This method has been extensively compared in a clinical population by these authors and excellent clinical protection of the heart was noted (4). Episodes of heart block from coronary sinus catheters was virtually eliminated in their series.

Although appealing in its simplicity, several problems with right atrial retrograde cardioplegia exist. Of foremost concern is the distension of a flaccid right ventricle to 50 mm Hg of pressure and the ensuing stretch of myocardium that this entails. Although the right ventricle can be rapidly decompressed by manually squeezing it after administration of cardioplegia, nevertheless, cardioplegia administration via this retrograde route is a prolonged procedure and detrimental effects on right ventricular function need to be clinically studied. We have looked at this problem in the controlled setting of the laboratory and have previously reported that right atrial cardioplegia, while adequately protecting the left heart, results in post bypass right ventricular distension and diminished right ventricular function (9) (Tables 2 and 3). We believe that this effect has occurred not only because of the distension of the right ventricle but also secondary to basic anatomic relationships as outlined by Bretschneider. The coronary venous system of the right ventricle communicates with the right ventricular chamber through thebesian venous systems as

Table 2. Comparison of right ventricular (RV) and septal temperatures in hearts with multivessel coronary artery lesions – right atrial (RA) versus coronary sinus (CS) cardioplegia.

Type of cardioplegia	Temperature (°C)	
	RV	Septum
RA	22 ± 2.6	23 ± 5°
CS	18 ± 2°*	14 ± 2°*

$p < 0.05$ CS vs. RA.

Table 3. Comparison of right ventricular (RV) systolic shortening in hearts with multivessel coronary artery lesions – right atrial (RA) versus coronary sinus (CS) cardioplegia.

Type of cardioplegia	RV Systolic shortening (mm)	
	Baseline	60 minutes post bypass
RA	3.0 ± 1	1.4 ± 0.2
CS	2.4 ± 1	2.0 ± 0.7

$p < 0.05$ vs. baseline.

well as the coronary sinus; all structures entering the right ventricle and atrium by definition must be pressurised at 50 mm Hg during right atrial cardioplegia. Thus, flow through the venous system of the right ventricle must be minimal during right atrial cardioplegia delivery, resulting in probable inadequate protection of the right ventricle. Conversely, flow to the left ventricle, if aortic drainage is provided, is probably excellent, as can be confirmed experimentally. In contrast, we have recently shown that right ventricular hypothermia and protection are both achieved in hearts with multivessel coronary artery lesions by using coronary sinus instead of right atrial cardioplegia (12) (Table 2). Clearly, the seeming contradiction between experimental and clinical results must be settled before this form of retrograde cardioplegia can be heartily recommended.

Coupled with the exciting innovations in retrograde coronary sinus perfusion during acute myocardial infarctions or ischaemia is the use of retrograde cardioplegia during emergent coronary artery bypass grafting for ongoing myocardial infarction or ischaemia. Recent work by Gardner and his colleagues (16) has demonstrated that infarct extension can be significantly reduced from that obtained by antegrade cardioplegia by using the retrograde coronary sinus route. Certainly, the coupling of a single catheter to deliver retrograde perfusion in working and beating hearts while then delivering retrograde cardioplegia in the same heart during coronary artery bypass grafting is appealing to surgeon and cardiologist alike.

Commensurate with this exciting experimental and clinical work on retrograde cardioplegia has been a rapid development of new catheter designs to deliver retrograde cardioplegia safely into the coronary sinus. At least four working groups (20, 26, 27), currently have catheters either being used experimentally and/or clinically and obtainable from major international companies. Important aspects of catheter design include methods of holding the catheter within the coronary sinus atraumatically without resorting to suture; methods of catheter introduction transatrially without resorting to an atriotomy; incorporation of fail safe pop-off valving to prevent over-distension of the coronary sinus and methods of measuring coronary venous pressure during the infusion cycle. Certainly, additional work needs to be done in all these areas before the optimal catheter design is produced. Nevertheless, even the simplest Foley catheter produces good results if appropriate steps to prevent over-distension of the balloon within the coronary sinus and avoiding too high pressure or flow of the cardioplegic agent are taken.

Future trends

Retrograde cardioplegic protection of the myocardium is entering a time of rapidly increasing interest. Much investigation needs to be performed in determining optimum pressures for retrograde cardioplegia, solution composition, and whether retrograde cardioplegia should be best administered as a bolus or in a continuous drip fashion. Further investigation needs to be performed as to whether the heart should be stopped with antegrade cardioplegia and then slowly protected with retrograde cardioplegia to produce more efficient and even core cooling.

In the same light, the clinical availability of retrograde cardioplegia must be improved. Administration of retrograde cardioplegia must be as easy as antegrade cardioplegia or its widespread use will probably not become possible even if experimental and clinical benefits are otherwise produced. Long-term studies of the coronary venous system must also be undertaken to determine if retrograde cardioplegia with its high potassium concentrations has any effect on fibrosing the coronary veins.

Certainly, exciting new advances will be reported as more groups become involved with retrograde coronary sinus cardioplegia. Indeed as this chapter goes to press four papers on retrograde cardioplegia have been accepted for presentation at the 1985 American Heart Association Scientific Sessions.

Conclusions

Utilisation of the coronary venous system to protect the ischaemic myocardium during aortic cross-clamping, while not a particularly new technique, seems to be experiencing a much deserved resurgence of interest both in the clinical and experimental arena. Previous investigations have shown that myocardial protection in the normal heart is at least as good with coronary sinus cardioplegia as with antegrade cardioplegia and indeed retrograde cardioplegia appears to be superior in most aspects to antegrade cardioplegia whenever coronary artery disease is present. Retrograde cardioplegia appears to offer the surgeon an improved method of ensuring cardioplegic delivery to jeopardised myocardium and perhaps even limiting infarct extension during acute myocardial infarctions and revascularisation (Table 4).

Table 4. Areas of proven worth of retrograde cardioplegia.

1) Aortic valve replacement
2) Coronary artery bypass for occluded or stenotic coronary arteries
3) Revascularisation of acute myocardial infarction

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Technological aspects of coronary sinus interventions

W. Mohl and P. Simon

Retroperfusion techniques as applied in the 1980s have become available thanks to the enormous progress in catheter and balloon technology. While Beck's procedure was a purely surgical approach based on the arterialization of the coronary sinus through an arteriocoronary venous fistula and subsequent ligation of the coronary sinus, present day coronary sinus interventions essentially draw on the potential of interventional cardiology to contain the risks of acutely jeopardized myocardium during ischemia through less invasive techniques, such as catheterization of the coronary sinus.

Current procedure in coronary sinus catheterization

Coronary sinus (CS) catheterization has long proved efficient in metabolic and electrophysiological studies. A permanent insertion of pacing leads has been shown to produce thrombosis of the coronary sinus. This has been found to be due to mechanical trauma as much as to changes in the CS environment, brought about by the electric current. According to our own experience from multiple experimental series and preliminary human studies no coronary sinus traumatization is found provided that adequate heparinization is available (4). In early dog series with latex balloons we did, however, observe ruptures of the coronary sinus stemming from excessive dilatation of the coronary sinus and subsequent hemorrhages extending into the surrounding myocardium. Just recently Guerci reported on thrombosis of the CS brought about by the use of an elongated balloon without sufficient anticoagulation (3).

Thus, it appears essential to draw on "high-tech" balloon technology so as to prevent rupture of the endothelium or an overdistension of the coronary sinus entailing rupture of the CS and subsequent thrombosis. Both anticoagulation measures and a stable positioning of the catheter shaft appear indispensable. Muers has reported on reflexes originating in the coronary sinus (5). While hypertension and tachycardia have been found to be of minor importance in this respect, possible disturbances of AV conduction appear liable to turn into a major disadvantage of this method, which nevertheless deserves further exploration.

In explorative studies such as our own current PICSO study, catheterization of the CS for intraoperative cardioplegic retroperfusion has been found to be a relatively simple and convenient technique; in our current approach we use a purse-string suture to insert the catheter blindly and through manual control before going on bypass in order to prevent air locks. Thereafter the catheter is under visual control and is fixed tightly to stay in that specific position.

Percutaneous approaches to CS catheterization in humans as reported by Gore appear to be feasible, also in acute emergency settings (2).

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CS interventions and blood trauma

Since neither PICSO nor retroinfusion draw on extracorporeal blood shunting, blood and tissue trauma must be assumed to be due to an increase in coronary venous pressure and/or inadequate catheter placement itself. It will be the challenge of future studies to get a firm grasp on this potential hazard. In various SCSR studies some degree of hemolysis has been found to be due to an active and external pumping of arterial blood. Furthermore, retroperfused blood has been demonstrated to enter the coronary sinus in the form of jets with critical velocities, which are hypothesized to be detrimental to cell linings (1). The discovery of a method to cope with this hazard remains the challenge of further research activities in the field of polymer chemistry and catheter technology.

Pump systems

Instrumentation used for coronary sinus interventions can be relatively simple, as is the case with the electromagnetically driven pneumatic PICSO pump, or may be slightly complicated as in the case of SCSR, which is more complex due to its blood pumping capacity. Both pumps make use of the monitoring of physiologic parameters to optimize the effectiveness of the intervention (PICSO – coronary sinus pressure; SCSR – electrocardiogram). Further advances in the technology of pump systems are therefore necessary if we are to develop a fail-safe and efficient system that can be supervised by alert intensive care staff. In fact, it will take a whole new era in pump technology if retroinfusion of drugs and/or cardioplegia are to be integrated into the systems currently available.

Conclusion

Great progress has been made in the application of coronary sinus interventions in humans. Currently these interventions are the subject of extensive evaluation regarding the necessity of their adaptation to the specific requirements of human settings. It needs to be said that the systems currently available are merely investigational devices which need further refinement and modifications for their ultimate use in routine settings. If these systems are to be of any use in clinical practice, the manufacturer has to seek the physicians' feedback. Both the expert working in the field of CSI technology and the research physician interested in the human application of any such new and promising technique are still in the process of learning. These two essentially share the challenge of developing fully fledged and efficient approaches, their interest thus being mutual and their efforts interrelated. In this endeavour it will lie with the technologists to design and offer to the clinician state-of-the-art systems, while it will be the clinician's responsibility to evaluate their significance in coronary sinus interventions.

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Pros and cons – coronary sinus intervention vs. conventional therapy

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Introduction

Since the introduction of coronary sinus techniques to treat ischemic syndromes by Claude Beck in 1948 (1), numerous investigators have attempted to develop techniques to utilize the unique circulation of the coronary veins (35). Nevertheless, there remains considerable uncertainty about the usefulness of these therapeutic modalities, due to limited clinical experience. At present there are four techniques under active investigation: coronary venous retroinfusion of cardioplegia, selective coronary venous retroinfusion, synchronized retroperfusion, and pressure controlled intermittent coronary sinus occlusion. Each has its own distinct advantages and disadvantages, which will be discussed individually. Since the latter two techniques are still in experimental animal studies, I will merely speculate on potential clinical applications for these techniques.

Retroinfusion of cardioplegia

The technique of retroinfusion of cardioplegia during open heart surgery has been proposed as a means to gain access to the myocardium in the setting of severe coronary disease and hypertrophy. The rationale is that in these settings inadequate tissue perfusion occurs as a result of antegrade perfusion and a more direct, less obstructive perfusion can occur retrogradely. The studies of Poirier, Lolley, Menasche, Fabiani, and others have demonstrated improved perfusion that resulted in less leakage of cardiac enzymes, less arrhythmias, and improved hemodynamic parameters (8, 28, 31, 38). These clinical studies have also emphasized improvement in subjective and objective measurements of left ventricular function.

Despite the treatment of hundreds of patients with retroinfusion, few randomized controlled trials have been conducted to evaluate this technique in comparison to conventional antegrade delivery of cardioplegia. Perhaps this is due to the relatively effective means of delivering cardioplegia currently employed or to concerns about the hazards of coronary sinus delivery. Potential hazards of retrograde infusion include a longer time to arrest the heart due to the need for selective cannulation, damage or trauma to the coronary sinus, and concerns regarding the inability to protect the myocardium in the right coronary artery distribution (Table 1). In addition, if excessive pressure is generated in a flaccid heart, potential damage might occur. Yet in experienced hands none of these complications are common. At present there appears to be adequate clinical information to warrant further evaluation, and clinical trials should be undertaken. Perhaps the most

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Table 1. Antegrade vs. retrograde cardioplegia.

Cardioplegia	Antegrade	vs.	Retrograde
Pros	Proven effective Quicker diastolic arrest		More uniform delivery Better visualization during aortic surgery
Cons	Potentially inadequate in hypertrophy or severe CAD Coronary artery damage		Slower diastolic arrest Coronary sinus damage May be inadequate in RCA disease

likely application of this technique will be in the subsets of patients in whom antegrade cardioplegic delivery is likely to be inadequate (e.g., severe hypertrophy or coronary artery disease) (Table 1).

Selective coronary venous retroinfusion

This technique involves the direct anastomosis of a bypass conduit or internal mammary artery to a coronary vein with direct retroperfusion of a localized region of the myocardium. The principle is similar to the original studies by Beck except that selective arterialization allows for better venous drainage and does not interfere with non-ischemic regions. Studies by Chiu, Hochberg, and Moll (3, 18, 36) have demonstrated restoration of normal flow and reduction in infarct size. However, the high venous pressure and potentially adverse effects on veins and microvasculature is a potential area of concern. Continued investigation and clinical experience may prove this technique to be useful in selected patients in whom adequate coronary bypass grafting or internal mammary artery grafting cannot be achieved.

Coronary sinus interventions – SRP and PICSO in acute myocardial infarction
(Tables 2 and 3)

Synchronized retroperfusion (SRP) was first introduced by Meerbaum and Corday in the early 1970s and is described in detail in other reports (36). The fundamental principle of this technique is to deliver oxygenated blood to the ischemic myocardium by retrograde perfusion during diastole allowing for venous drainage during systole. Experimental studies to date have clearly shown that the technique reduces infarct size and results in improvement in regional and global left ventricular function as early as 30 minutes after institution of the technique (2, 7, 9, 43). In addition, Smith demonstrated the effectiveness of SRP in the setting of antegrade reperfusion in a baboon model where SRP was begun early after coronary occlusion (43). Whether additional benefit would be realized if SRP were instituted at the time of reperfusion has not yet been studied. Additionally, it has been shown that retroperfusion of antiarrhythmic drugs may provide a unique way to deliver high concentrations of these agents without adverse systemic effects (7). A preliminary report of retrograde perfusion of streptokinase has shown a more rapid dissolution

Table 2. Coronary sinus interventions (CSI): Synchronized retroperfusion (SRP) vs. pressure controlled intermittent coronary sinus occlusion (PICSO).

	SRP	vs.	PICSO
Pros	Reduces infarct size		Same
	Improves LV function		Same
	Beneficial during reperfusion		Same
	Direct delivery of drugs		–
	(e.g., antiarrhythmics, SK, etc.)		Hemodynamic monitoring
Cons	Coronary sinus selective cannulation		Same
	Arterial access necessary		–
	Potential hemolysis		–
	Potentially less effective in ischemia		Potentially less effective in ischemia
	Potentially less effective in RCA disease		Potentially less effective in RCA disease

Table 3. Acute myocardial infarction.

	CSI	vs.	Thrombolysis
Pros	Reduces infarct size		A more effective means of reducing infarct size
	Improves regional LV function		Same
	Is complementary to reperfusion		–
	Can deliver drugs (SRP)		–
	Hemodynamic monitoring (PICSO)		–
Cons	Invasive		Not necessarily invasive
	Coronary sinus damage		Significant risk of bleeding

of clot (30), while hypothermic retroperfusion has been of additional benefit in experimental studies (15).

Pressure controlled intermittent coronary sinus occlusion (PICSO) introduced by Mohl in 1981 has also shown great promise (33). Experimental studies have demonstrated a reduction in infarct size, as well as improvement in regional myocardial function (4, 34). More recently, Jacobs has demonstrated the additional benefit of PICSO in a reperfusion canine model (21). The principle of this technique is to temporarily occlude the coronary sinus in order to redistribute blood into the underperfused myocardium. While the exact mechanism is unknown, it is proposed that PICSO works by the washout of toxic metabolites and edema (32). Since no direct retroperfusion occurs, delivery of drugs is not possible without interruption of the PICSO cycle. However, important hemodynamic information is obtained from monitoring the coronary sinus occluded pressure (10, 22). Previous studies in a canine model have demonstrated a relationship between coronary sinus pressure and left ventricular systolic pressure while the rate of change in coronary sinus pressure during occlusion related to coronary blood flow. Studies in man have shown that the coronary sinus diastolic pressure closely parallels left ventricular diastolic

pressure. Ongoing studies suggest that other indices of myocardial function could be assessed, such as infarct size and the area at risk of infarction.

The potential of these techniques in acute myocardial infarction seems great; however, it is important that we view them in light of other emerging and established modalities to treat infarction. For the past 15 years a major research focus has been on methods to reduce infarct size (16). Initially, research centered upon means of reducing myocardial oxygen consumption. A number of interventions have been explored and include: beta-adrenergic blockade, coronary vasodilators, peripheral vasodilators, intra-aortic counterpulsation, inotropic agents, and inhibitors of lipolysis such as glucose-insulin-potassium. Experimental evidence has shown that all of these approaches can reduce infarct size. However, clinical studies have been less convincing. While β-blockers have been used in secondary prevention, the evidence for a significant reduction in infarct size is conflicting. The Swedish Metoprolol trial has shown a significant reduction in mortality in patients given Metoprolol within 12 hours of a myocardial infarction. In addition, there has been evidence for lower LDH levels and improved survival [17]. However, the Milis study found no benefit from propranolol although the average time to institution of therapy was relatively late (e.g., 8 hours) (41). Perhaps one explanation for this discrepancy is that propranolol has been shown to reduce ST-segment elevation when given to patients who have a partially patent coronary vessel and not in those who have total coronary occlusion (13). Studies of vasodilators have also shown mixed results. A positive effect of nitroglycerin was shown in a study from Johns Hopkins where nitroglycerin was administered within 10 hours of acute myocardial infarction (11). However, other studies have not confirmed this observation. Nitroprusside has also shown a variable response as reported in the V.A. randomized trial (45). Pooled data from seven nitroglycerin trials and two nitroprusside studies show that nitroglycerin may reduce mortality by 30% and appears to be more effective than nitroprusside (45). Counterpulsation, intra-aortic or external, has been used extensively in unstable angina and cardiogenic shock but has not gained wide acceptance in the patient with acute myocardial infarction since studies have not conclusively shown a significant benefit from this invasive technique (26). Glucose, potassium, and insulin by enhancing oxygen phosphorylation and reducing free fatty acid oxidation might reduce myocardial oxygen consumption. While experimental studies have shown improvement in left ventricular function, clinical trials have not. Yet a significant reduction in ventricular ectopy has been observed by some (42).

The use of techniques to reduce myocardial oxygen consumption during acute myocardial infarction seems justified. Yet as briefly outlined above, currently employed techniques have had only a modest effect on left ventricular function. For this reason, recent studies have focused on means of improving antegrade perfusion to the ischemic myocardium. On the basis of studies in dogs it is clear that early reperfusion of an occluded coronary artery will reduce infarct size (39). While Herrick initially suggested coronary thrombosis as a cause of myocardial infarction, this concept was not generally accepted until DeWood and colleagues demonstrated that total occlusion of a coronary artery occurred in more than 90% of patients (6). Numerous observational studies have shown that intracoronary or intravenous streptokinase can dissolve intracoronary thrombosis and restore coronary flow (25, 40). Recent randomized trials have confirmed a beneficial effect. Kennedy and associates showed a reduction in mortality at 6 months when streptokinase was given intracoronarily (24). More recently the ISAM trial (20) and the Gissy trial (12) have demonstrated significant reduction in LV function or mortality with the

use of intravenous streptokinase. Other newer thrombolytic agents such as tPA appear to be even more effective than streptokinase and may have promise (44). On the basis of these trials it seems likely that thrombolytic therapy will become the standard treatment for patients with acute myocardial infarction.

In addition, there has been great interest in the use of angioplasty either alone or in combination with thrombolysis during acute myocardial infarction, as observational studies have demonstrated its feasibility (19). A recently reported randomized trial from O'Neill and colleagues suggests that PTCA may be superior to intracoronary streptokinase. They demonstrated that PTCA was more effective in improving left ventricular function and reducing subsequent angina (37). The effect on mortality was not significant but longer term trials are necessary to evaluate this endpoint.

It is clear from these data that coronary sinus interventions need to be assessed in the setting of thrombolysis with or without angioplasty. Experimental data presented elsewhere have shown that SRP and PICSO may well have an adjunctive role in acute myocardial infarction. One of the major problems of all reperfusion techniques is the need to restore flow as early as possible. Techniques that may allow a longer time to institute acute interventions and reduce infarct size would clearly have a role in therapy. Importantly, techniques that would enhance the effect of antegrade reperfusion by reducing reperfusion "injury" would also be useful. Experimental data would suggest that both SRP and PICSO may fulfil these objectives.

Any therapy must be assessed in the context of its risks and the ease of institution of the therapy. Since both SRP and PICSO are invasive they are unlikely to be routinely applied if thrombolytic agents can be given intravenously without significant risk. However, in subsets of high risk patients (e.g., anterior MI, CHF, or shock) coronary sinus intervention (CSI) would appear to have an important adjunctive role to current therapy. Clinical experimentation is now necessary in order to place these interventions in context with other evolving therapeutic approaches.

CSI in unstable angina

The benefit of CSI in unstable angina remains much more speculative since little experimental evidence or clinical experience is currently available. While improvements in left ventricular function have been demonstrated during prolonged ischemia with both techniques, prevention of recurrent brief angina has not been extensively studied. One experimental canine study by Jacobs et al. would raise concern that PICSO may not be effective in the setting of acute intermittent coronary occlusion (23), while the clinical observations of Gore would suggest that SRP may be effective in the setting of unstable angina (14). The evidence to date is only preliminary and we again need carefully designed clinical studies in order to understand the potential use of these techniques in unstable angina. Their benefit must be placed in context with other currently used techniques to manage unstable angina such as β-blockers, calcium antagonists, intravenous nitrates, anticoagulation, and intraaortic balloon counterpulsation. Like intra-aortic balloon counterpulsation, coronary sinus interventions would most likely find an application as a holding technique to stabilize patients with recurrent chest pain prior to further definitive revascularization procedures.

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CSI: temporary support or long-term therapy

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Beck's era: long-term therapy

Some 40 years ago Claude Beck and his colleagues dedicated numerous research activities to the evaluation of whether coronary sinus occlusion and arterialization were to be effective techniques in long-term treatment of myocardial ischemia. Eventually these studies led to the application of the Beck II procedure in about 200 patients with coronary artery disease. Beck's procedure was based on a major surgical intervention involving CS ligation and was suggested to provide *long-term relief.* While early applications gave rise to great optimism, in the long run failure to obtain homogeneous results and the rise of coronary bypass graft surgery led to a shift in interest, factors generally considered to be the main reasons why the technique was virtually abandoned in the years to follow.

Today's concept of providing temporary support

Just some 10 years ago the scientific community regained interest in the route via the coronary sinus as a promising modality when access to jeopardized myocardium is severely impaired. While during Beck's era the technique was supposed to provide long-term therapeutical relief, today's idea is to exploit the method's benefits for the provision of *temporary support* in acute settings. This concept owes much of its feasibility to the rise of interventional cardiology and the enormous technological advances of recent decades. From this favourable context most diverse theories and techniques have evolved, all of which aim at minimal interference and maximum benefit in terms of improved function and maintenance of myocardial viability. SRP, PICSO and retroinfusion, all of which have already been discussed at great length, have been found to provide temporary support in situations of acute ischemia, SRP and PICSO being applied in regional ischemia during cardiac interventions, and retroinfusion providing benefit in global ischemia. SRP has come to be considered a useful temporary circulatory assist, which has been supplemented with hypothermia and retrograde drug infusions. Opposed to this, PICSO is a simpler device, which has been found to benefit ischemic myocardium by improved washout of deleterious metabolites and increased flow to underperfused zones. As reported elsewhere numerous studies have found PICSO to significantly reduce infarct and support cardiac function and viability. What, in fact, singles it out from other approaches is the fact that due to its intermittent nature it appears to best meet the requirement of noninterference and low invasiveness. As to the perspective of future applications of this method in long-term therapy it must, however, be said that so far maximum length of application in settings of regional ischemia has been 6 hours and that so far there are no

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investigational data to hand as to how patients might benefit from prolonged and repeated interventions in chronic settings for therapeutical ends.
With regard to drug administration there has always been the question of whether antegrade or intravenous administration can be delivered to the regions at greatest risk. Thus, much indicates that a fruitful era lies in store for retrograde coronary venous drug administration or intermittent coronary sinus occlusion, both of which have been found to be successful in the presence of a left artery occlusion.
This takes us right to the future perspectives of CSI, which have been addressed in great detail in the present volume. In summary we foresee two branches of future applications:

1. Settings of acute myocardial jeopardy such as myocardial infarction (with or without lysis therapy), unstable angina, PTCA and perioperative settings.
2. Inoperable settings of chronic myocardial ischemia.

Future perspectives: long-term therapy

As indicated in item 2 above we hypothesize that coronary sinus interventions might also prove beneficial as a *long-term therapeutic* tool in the treatment of chronic heart disease. Such an approach would indeed mean a great leap ahead and yet at the same time would take us back to Beck's initial idea of providing long-term therapeutic relief. While such a concept may at first glance appear somewhat far-flung, successful applications of CSI with regard to reinforcing the action of medication and with regard to a reversal of metabolic dysfunction have indicated that this claim of ours might eventually be found legitimate. It remains, however, necessary to establish the presence of these beneficial effects over prolonged periods of time in humans. Should respective investigations confirm our proposition, present state-of-the-art technologies will permit the prolonged and repeated application of CSI in long-term therapeutical patient management. Inconveniences to the patient are assumed to equal those chores cardiac transplant recipients have to take upon themselves (exposure to biopsy at regular intervals). Provision of long-term relief is also assumed to require repetition of CSI at regular intervals. Total length of therapy and length of individual intervals are yet to be established. The rationale behind this idea is our assumption that CSI, provided that they will be found to enhance drug therapy also in cases of chronic ischemia, will not only protect ischemic myocardium but, if performed repeatedly and over prolonged periods of time, will re-establish a steady state of myocardial metabolism, and bring about prolonged improvement of myocardial performance and hence, serve as a valuable therapeutic tool.

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