The salvage potential of coronary sinus interventions: Meta-analysis and pathophysiologic consequences

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Objectives: Intermittent coronary sinus occlusion has been described to be effective in salvaging ischemic myocardium. This meta-analysis aims to review the efficacy of intermittent coronary sinus occlusion and intermittent coronary sinus occlusion in combination with retroperfusion of arterial blood as methods of myocardial salvage.

Methods: A Medline search was performed to review the published literature on intermittent coronary sinus occlusion. The study inclusion criterion was a randomized, placebo-controlled trial with area of infarction (expressed as a percentage of the area at risk) as the primary end point.

Results: Seven experimental trials comprising 125 test animals were found that analyzed the effects of intermittent coronary sinus occlusion on ischemic damage during coronary occlusion. A further 5 studies comprising 88 animals were designed to evaluate the effect of intermittent coronary sinus occlusion in combination with retroperfusion of arterial blood on the infarct size. A meta-analysis of the 7 studies analyzing the effect of intermittent coronary sinus occlusion revealed a significant reduction in infarct size of 29.3% in the treatment group compared with that in the placebo group ($P < .001$; 95% confidence interval, -40.9 to -17.7). A meta-analysis of the 5 trials analyzing the effect of intermittent coronary sinus occlusion in combination with retroperfusion revealed a reduction in infarct size of 39.4% in the treatment group compared with that in the placebo group ($P < .001$; 95% confidence interval, -48.9 to -29.9). Comparison between intermittent coronary sinus occlusion and intermittent coronary sinus occlusion in combination with retroperfusion of arterial blood showed no statistical difference ($P = .19$). An inverse relationship between achieved coronary sinus pressure increase per minute and infarct size could be found in the intermittent coronary sinus occlusion group ($r = -0.92$; $P < .007$), whereas in combination with retroperfusion, there was a negative correlation both between achieved coronary sinus pressure and the amount of the retroperfusate and myocardial salvage ($r = -0.97$; $P < .004$).

Conclusions: The use of intermittent coronary sinus occlusion and intermittent coronary sinus occlusion in combination with retroperfusion of arterial blood

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significantly decreases ischemic damage during coronary occlusions. Intermittent coronary sinus occlusion in combination with retroperfusion exhibits no significant profit in salvaging the ischemic myocardium in comparison with that provided by intermittent coronary sinus occlusion alone.

The concept of arterialization of the cardiac venous system to increase the flow of oxygenated blood to ischemic myocardial tissue was suggested more than 100 years ago[1] and has since been modified with the development of new technologies. Initial attempts of permanent retroperfusion of the coronary sinus by means of anastomosis to an arterial vessel were soon truncated because of ultrastructural damage of the wall of the coronary sinus caused by drainage disruption.[2,3] Moreover, with the birth of the coronary artery bypass grafting era and the further development of percutaneous transluminal coronary angioplasty, the concept of selective retroperfusion was discarded. Attempts to introduce coronary sinus interventions clinically by interventional cardiologists also have been abandoned.

The advent and current praxis of off-pump revascularization and its potential benefits through avoidance of extracorporeal circuits again draws interest to myocardial protection through the coronary sinus. It is well understood that occlusion of a coronary vessel might create regional ischemia and subsequently cause an inflammatory response.[4] This might be one of the reasons why the clinical benefits of this procedure are still difficult to detect.[5]

Several retroperfusion methods have been advocated to ameliorate myocardial ischemia during off-pump surgery.[6,7] Lazar and colleagues[8,9] also suggested that the simple method of transient coronary venous pressure increase caused by coronary sinus occlusion might at least be equivalent to that seen with retroperfusion techniques. There is ample evidence that coronary sinus intervention salvages ischemic myocardium during myocardial infarction.[10-12]

Although intermittent coronary sinus occlusion (ICSO), pressure-controlled intermittent coronary sinus occlusion (PICSO), synchronized retrograde perfusion (SRP), and simplified retroperfusion (SR) have all been described to be effective in salvaging ischemic myocardium in several experimental models of coronary artery occlusion,[13,14] the mode of action of these interventions remained speculative. The common denominator of all coronary sinus interventions is the temporal increase in coronary venous pressure through temporal occlusion of the outflow, retroperfusion of arterial blood, or both. ICSO is a simple method that occludes the coronary sinus intermittently through inflation and deflation of a balloon-tipped catheter that is positioned in the orifice of the coronary sinus. This results in a redistribution of coronary sinus blood flow within the venous compartment to the ischemic myocardium through changes in pressure gradients throughout the coronary venous system.[15] The balloon catheter is connected to a pneumatic pump that automatically increases and decreases pressure in the coronary venous system according to a preset cycle. The SRP and SR systems are modified ICSO techniques that actively pump arterial (SRP) or venous (SR) blood into the coronary sinus and have been used clinically for myocardial protection during high-risk angioplasty.[16,17] Systems using selective retroperfusion and synchronized suction of the oxygenated blood represent an extended version of the SRP technique.[18] Further developments include the left ventricle to coronary sinus shunt, which is a left ventricle–powered system that provides a graded systolic retroperfusion of the coronary sinus.[7] Experimental and clinical studies have previously demonstrated all these techniques to significantly increase blood flow to the ischemic myocardium and thus reduce infarct size.[7,13,19,20]

The aim of this study was to systemically review published evidence of coronary sinus interventions in the medical literature and to perform a meta-analysis of available randomized trials to assess the efficacy of ICSO-PICSO and ICSO in combination with retroperfusion of arterial blood as myocardial salvage in terms of reduced infarct size. Furthermore, we sought to perform a comparison between both procedures and to draw pathophysiologic conclusions. This evidence-based analysis could be the basis for matching an old and almost forgotten but attractive concept of myocardial protection and the new techniques of off-pump surgery, thus clarifying the clinical benefit of both procedures.

Methods

Identification of Trials and Inclusion Criteria

A Medline search was conducted for all articles published until 2003 which assessed the effects of coronary sinus interventions on myocardial salvage during acute ischemia in experimental and clinical trials. The following terms were used for the search: (1) "pressure-controlled intermittent coronary sinus occlusion" (37 reports identified); (2) "intermittent coronary sinus occlusion" (42 reports identified); (3) "PICSO" (15 reports identified); (4) "ICSO" (12 reports identified, of which 8 are related to the cardiovascular system); (5) "coronary sinus retroperfusion" (73 reports identified); (6) "intermittent coronary sinus retroperfusion" (16 reports

identified); and (7) "synchronized retrograde perfusion" (11 reports identified). Relevant articles were identified from the title or abstract (when available) for further review. Bibliographies of all retrieved articles were evaluated for other relevant references. Multiply yielded reports were considered once such that a total of 100 articles remained for further review.

Two authors independently evaluated all 100 relevant reports identified by the searches. The study inclusion criterion was a randomized, placebo-controlled trial with area of infarction (expressed as a percentage of the area at risk) as the primary end point. Studies with application of ICSO without other techniques except for retroperfusion of arterial blood were included in the analysis. Reports of ICSO and ICSO in combination with retroperfusion of arterial blood were handled separately for a separate analysis. All information retrieved from the reports were tabulated by one reviewer and subsequently confirmed by a second reviewer.

Data Extraction

The following information was assembled for each study: (1) publication data, first author's last name, and year of publication; (2) study design; (3) characteristics of treated versus placebo group (including number of subjects in each group); and (4) target parameter as area of infarction (expressed as a percentage of the area at risk), including mean values and either SD or SEM. All reported SEMs were converted to SDs as follows:

$$SD = SEM \times \sqrt{n}. \quad (1)$$

Statistical Analysis

All similar studies were pooled by using weighted mean differences, with 95% confidence intervals on the basis of normal distribution. Heterogeneity of study results was tested by estimating the between-study variance (BSV) by using restricted maximum likelihood and testing the null hypothesis of a BSV of 0; a P value of less than .05 was considered as indicating the use of random-effects models. Comparison between the weighted mean differences of ICSO and ICSO in combination with retroperfusion of arterial blood was performed by using a z test.

The linear regression test of Egger and associates[21] was used to test the null hypothesis of the absence of publication bias. This test performs a linear regression of the standardized effect estimates (mean difference/SE) on SEs of all trials. The estimated intercept parameter is then used to measure asymmetry, with a significant difference from 0 being assumed to indicate publication bias. A negative intercept is considered to indicate smaller studies to be associated with bigger effects.

To determine the range of results that would be obtained with varying plausible assumptions, we evaluated the sensitivity of the weighted results on the basis of (1) omission of particular studies and (2) varying the assumptions on BSV. By using the jackknife technique,[22] the analysis was repeated multiple times, with the data from a single study removed each time from the data for the entire group of studies. This allowed us to determine the influence of each single study on the pooled result. In a second sensitivity analysis, we used the Thompson plot,[23] which indicates the effect of the choice of statistical method on the analysis. To construct a Thompson plot, the analysis is repeated by changing the percentage of weight allocated to each trial from allocating equal weight to each trial, which corresponds to assuming infinite BSV, to weighting each study with the inverse of its variance, corresponding to assuming zero BSV. Although the y-axis of this plot corresponds to the pooled mean difference, the x-axis represents the following: *Assumed BSV/(Assumed BSV + Estimated BSV)*, and thus the value 0 of the x-axis corresponds to a fixed effects analysis, and the value 1 correlates to equal weighting of all studies. The Spearman nonparametric correlation coefficient was computed from the study means. SAS System Version 8.2 (SAS Institute Inc, Cary, NC) was used for statistical analysis.

Results

A total of 100 potential articles were identified from the Medline search and bibliography review. Eleven studies were designed to have a primary end point of area of infarction expressed as a percentage of the area at risk. Two of these trials were excluded from final analysis because of application of ICSO in combination with other techniques (Lazar and colleagues[24]: ICSO in combination with intraaortic balloon pump; Lazar and colleagues[25]: ICSO in combination with percutaneous bypass). A further 2 studies were designed to assess the efficacy of ICSO in combination with retrograde perfusion (Ropchan and coworkers[26]: ICSO in combination with intermittent coronary sinus retroperfusion; Martin and associates[7]: ICSO in combination with left ventricle to coronary sinus shunt). Consensus was reached between the 2 reviewers for final inclusion of the remaining 7 trials in the meta-analysis analyzing the efficacy of ICSO in reducing infarct size. A total of 125 subjects were included in the analysis. Details regarding the included studies can be found in Tables 1, *A*, and 2, *A*.

Of the 11 trials designed to assess the area of infarction as a primary end point, 5 studies were designed to evaluate the efficacy of ICSO in combination with retroperfusion of arterial blood on reduction of infarct size (thus 3 studies analyzed both the efficacy of ICSO and the efficacy of ICSO in combination with retrograde perfusion). These 5 studies were analyzed in an additional meta-analysis, comprising a total of 88 animals. Details regarding the included studies are tabulated in Tables 1, *B*, and 2, *B*.

The meta-analysis of the 7 studies analyzing the effect of ICSO on the infarct size revealed a significant reduction in infarct size of 29.2% in the treatment group compared with that in the placebo group (weighted mean difference between the ICSO and control groups, −29.3; 95% confidence interval, −40.9 to −17.7; $P < .0001$; Table 3). The test of heterogeneity indicated a significant difference of BSV from zero ($P < .0001$), thus implying the use of a random-effects model. The linear regression test of Egger and associates[21] revealed a negative yet not significant intercept term in the linear regression test for publication bias (intercept, −13.2; $P = .16$). Thus the linear regression test shows a tendency of publication bias and overestimation of the pooled mean difference; however, this trend is not signifi-

TABLE 1. Summary of study design

A. Intermittent coronary sinus occlusion

Source	Duration of occlusion/ICSO/ reperfusion	Duration of inflation/deflation	Achieved coronary sinus pressure
Mohl and coworkers, 1984[20]	15 min after CA occlusion: 6 h ICSO, no reperfusion	15.0 ± 3.0 s/4.0 ± 2.0 s	Mean, 44.0 ± 7.0 mm Hg
Zalewski and coworkers, 1985[27]	3 min after CA occlusion: 6 h ICSO, no reperfusion	15.0 s/4.0 s	Peak: 59.0 ± 4.0 mm Hg
Guerci and coworkers, 1987[36]	30 min after CA occlusion: 2.5 h ICSO, followed by 8–12 d reperfusion	10.0 s/5.0 s	Peak: 43.0 ± 5.0 mm Hg
Ikeoka and coworkers, 1990[14]	1 h after CA occlusion: 3 h ICSO, no reperfusion	13.0 ± 3.0 s/5.0 s	Peak: 56.0 ± 7.0 mm Hg
Feindel and coworkers, 1991[34]	Immediately after CA occlusion: 4 h ICSO, followed by 1 h reperfusion	5.0 s/5.0 s	Mean: 17.1 ± 6.4 mm Hg
Lazar and coworkers, 1992[37]	Immediately after CA occlusion: 90 min ICSO, followed by 30 min ischemic arrest and final 1 h reperfusion	8.0 s/4.0 s	Peak: 52.0 ± 3.0 mm Hg
Aldea and coworkers, 1996[13]	Immediately after CA occlusion: 90 min ICSO, followed by 60 min cardioplegic arrest and final 3 h reperfusion	10.0 s/4.0 s	Peak: 40–50 mm Hg

B. Intermittent coronary sinus occlusion in combination with retroperfusion of arterial blood

Source	Duration of occlusion/ICSO + retroperf/reperfusion	Duration of inflation/ deflation	Achieved coronary sinus pressure	Rate of retroperf
Feindel and coworkers, 1991[34]	Immediately after CA occlusion: 4 h ICSO + retroperf, followed by 1 h reperfusion	5.0 s/5.0 s	Mean: 56.1 ± 5.4 mm Hg	60.0 mL/min
Lazar and coworkers, 1992[37]	Immediately after CA occlusion: 90 min ICSO + retroperf, followed by 30 min ischemic arrest and final 1 h reperfusion	8.0 s/4.0 s	Peak: 45.0 ± 4.0 mm Hg	7.0 mL/min
Ropchan and coworkers, 1992[26]	Immediately after CA occlusion: 4 h ICSO + retroperf, followed by 1 h reperfusion	5.0 s/5.0 s	Mean: 51.0 ± 12.0 mm Hg	60.0 mL/min
Aldea and coworkers, 1996[13]	Immediately after CA occlusion: 90 min ICSO + retroperf, followed by 60 min cardioplegic arrest and final 3 h reperfusion	10.0 s/4.0 s	Peak: 40-50 mm Hg	50.0-200.0 mL/min
Martin and coworkers, 2000[7]	5 min after CA occlusion: 1 h ICSO + retroperf, followed by 3 h reperfusion	Not described	Mean: 15.0 mm Hg	111.0 ± 47.0 mL/min

ICSO, Intermittent coronary sinus occlusion; *CA*, coronary artery; *Retroperf*, retroperfusion of arterial blood.

cant. The range of weighted mean differences assessed by using the jackknife sensitivity analysis is calculated as −33.2 to −26.2 (weighted mean difference between the ICSO and control groups remained significant for all jackknife calculations, $P < .001$). The Thompson plot showed some dependence of the weighted mean difference on the

TABLE 2. Effects on myocardial infarct size

A. Effects of intermittent coronary sinus occlusion on myocardial infarct size

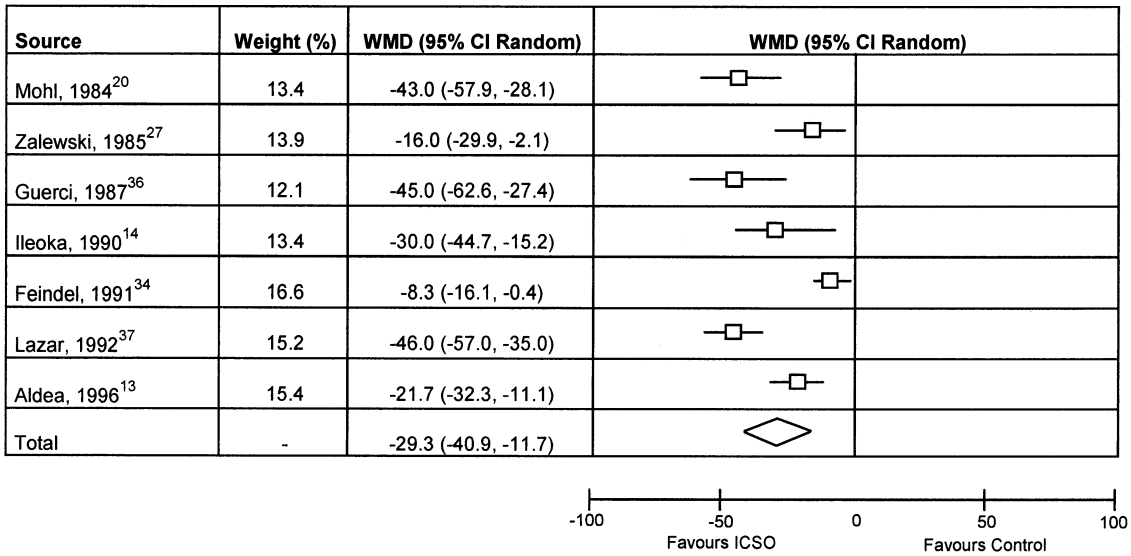
Source	No. of subjects (ICSO/control)	Subject type	Infarct size (%) ± SD (ICSO)	Infarct size (%) ± SD (control)
Mohl and coworkers, 1984[20]	13/12	Mongrel dogs	56.0 ± 25.2	99.0 ± 10.4
Zalewski and coworkers, 1985[27]	9/9	Mongrel dogs	84.0 ± 15.0	100.0 ± 15.0
Guerci and coworkers, 1987[36]	7/7	Mongrel dogs	30.0 ± 21.2	75.0 ± 10.6
Ikeoka and coworkers, 1990[14]	8/8	Mongrel dogs	39.0 ± 13.2	69.0 ± 16.7
Feindel and coworkers, 1991[34]	10/10	Yorkshire pigs	78.0 ± 10.2	86.3 ± 7.5
Lazar and coworkers, 1992[37]	10/10	Adult pigs	27.0 ± 12.6	73.0 ± 12.6
Aldea and coworkers, 1996[13]	6/6	Adult pigs	27.0 ± 7.3	49.0 ± 11.1

B. Effects of intermittent coronary sinus occlusion in combination with retroperfusion of arterial blood on myocardial infarct size

Source	No. of subjects (ICSO + retroperf/ control)	Subject type	Infarct size (%) ± SD (ICSO + retroperf)	Infarct size (%) ± SD (control)
Feindel and coworkers, 1991[34]	10/10	Yorkshire pigs	44.1 ± 12.9	86.3 ± 7.5
Lazar and coworkers, 1992[37]	10/10	Adult pigs	18.0 ± 6.3	73.0 ± 12.6
Ropchan and coworkers, 1992[26]	13/12	Yorkshire pigs	41.5 ± 15.0	80.5 ± 6.1
Aldea and coworkers, 1996[13]	6/6	Adult pigs	24.9 ± 4.8	48.5 ± 11.0
Martin and coworkers, 2000[7]	6/5	Yorkshire pigs	14.0 ± 3.1	51.0 ± 2.2

ICSO, Intermittent coronary sinus occlusion; *Retroperf,* retroperfusion of arterial blood.

TABLE 3. Effects of intermittent coronary sinus occlusion on myocardial infarct size



CI: confidence interval; WMD: weighted mean difference.

used weighting scheme (smaller effect estimated in a fixed-effects analysis with a weighted mean difference of −24.8; however, the significance between the ICSO and control groups remains, $P < .001$; Figure 1).

The meta-analysis of the 5 trials analyzing the effect of ICSO in combination with retroperfusion of arterial blood revealed reduction in infarct size of 39.4% in the treatment group in comparison with that in the placebo group (weighted mean difference between the treatment and control groups, −39.4; 95% confidence interval, −48.9 to −29.9; $P < .0001$; Table 4). The test of heterogeneity indicates a significant difference of BSV from zero ($P < .0001$), thus implying the use of a random-effects model. The linear regression test of Egger and associates[21] revealed no indication for publication bias (intercept, 0.41; $P = .98$). The range of weighted mean differences assessed by means of jackknife sensitivity analysis is calculated as −42.8 to −35.7 (weighted mean difference between the treatment

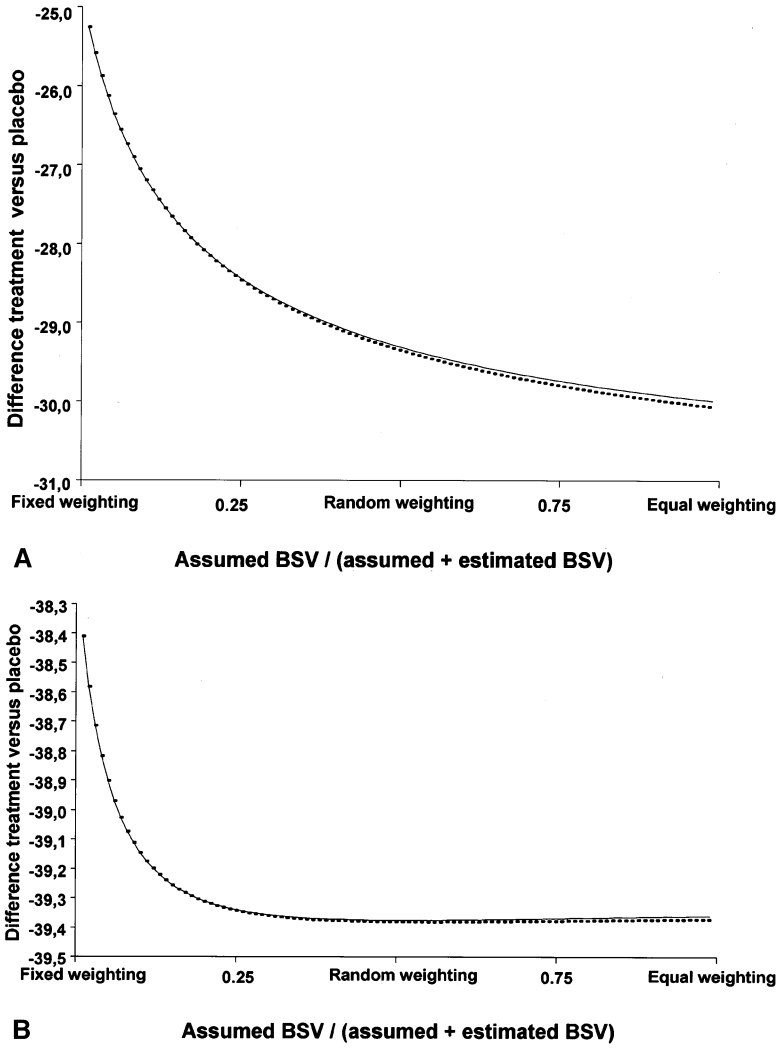


Figure 1. Thompson plot indicating the effect of the choice of statistical method on the analysis. A, ICSO versus placebo treatment: the curve implies dependence of the weighted mean difference on the used weighting scheme (smaller effect estimated in a fixed-effects analysis with a weighted mean difference of −24.8; however, the significance between the ICSO and control groups remains, $P < .001$). B, ICSO in combination with retroperfusion of arterial blood versus placebo treatment: the curve implies modest dependence of the weighted mean difference on the used weighting scheme only on the left extreme (ie, in case of fixed-effects analysis).

and control groups remained significant for all jackknife calculations, $P < .001$). The Thompson plot showed moderate dependence of the weighted mean difference on the used weighting scheme only on the left extreme (ie, in case of fixed effects analysis; note the scale of the y-axis).

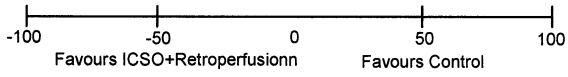
Comparison of the pooled mean difference between the ICSO and control groups with the pooled mean difference between the retrograde perfusion and control groups revealed no significant difference between ICSO and ICSO in combination with retroperfusion of arterial blood ($z = 1.316$, $P = .19$).

A correlation between achieved coronary sinus pressure per minute (ratio between coronary sinus occlusion and release) and infarct size showed a negative association in the ICSO group ($r = -0.70$; $P < .7$). Significance could be reached after eliminating the results reported by Zalewski and colleagues,[27] which apparently do not fit into the overall reported spectrum of evidence ($r = -0.92$; $P < .007$).

In contrast to the relationship of pressure increase and salvage potential in the ICSO group, ICSO in combination with retroperfusion resulted both in a negative correlation between achieved coronary sinus pressure and the amount

TABLE 4. Effects of intermittent coronary sinus occlusion in combination with retroperfusion of arterial blood on myocardial infarct size

Source	Weight (%)	WMD (95% CI Random)	WMD (95% CI Random)
Feindel, 1991[34]	19.5	-42.2 (-51.4, -32.9)	
Lazar, 1992[37]	19.7	-55.0 (-63.7, -46.3)	
Ropchan, 1992[26]	19.7	-39.0 (-47.8, -30.1)	
Aldea, 1996[13]	19.3	-23.6 (-33.2, -14.0)	
Martin, 2000[7]	21.9	-37.0 (-40.1, -33.9)	
Total	-	-39.4 (-48.9, -29.8)	



CI: confidence interval; WMD: weighted mean difference.

of the retroperfusate and myocardial salvage ($r = -0.97$; $P < .004$).

Discussion

Myocardial protection remains a sensitive issue, even in today's surgical practice. The technique of beating-heart surgery needs more than the brief occlusions of coronary arteries as applied in the interventional catheterization laboratory. According to the level of surgical complexity, repetitive occlusions in perfusion-dependent areas leave the myocardium unprotected to the dynamics of the ischemia-reperfusion injury.

Coronary sinus interventions are known to salvage ischemic myocardium, especially by limiting the infarct from its borders. The primary goal of all these approaches is not only to restore blood flow in the occluded vessels but also to salvage the damaged myocardium. In this study we systematically reviewed available data on coronary sinus interventions and performed 2 separate meta-analyses on the efficacy of ICSO alone and ICSO in combination with retroperfusion of arterial blood in reducing the area of infarction during acute ischemia assessed as a percentage of area at risk. We found an overall positive treatment response of ICSO in both analyses, with a reduction of 29.3% in animals undergoing ICSO versus a reduction of 39.4% in animals undergoing ICSO in combination with retroperfusion, both in comparison with the control group. Although both interventions significantly reduce infarct size and the fact that no further significance can be reached between the two methods, the available statistical data do not allow a further discrimination and are not helpful in determining which of the methods is superior.

The efficacy of ICSO in salvaging the ischemic myocardium during acute ischemia has been a matter of controversy for many years. Whereas the mechanism of retrograde coronary sinus perfusion of arterial blood and its positive effect on reducing the infarct size generally seem to be easily understood, doubts still remain regarding how a pressure increase in the coronary venous bed induced by ICSO alone might reduce the area of necrosis without any additional oxygen supply. In addition, ICSO summarizes a cohort of different methods, including variations in the timing of occlusions and the achieved pressures.

On the other hand, in interventions with retroperfusion of arterial blood, one would expect a diffusion of oxygen with subsequent salvage in a Krogh-like pattern from large veins throughout the infarct zone. This, however, does not seem to be the case because in both types of intervention, the pattern of myocardial salvage seems to be the reduction of the infarct zone from its borders. It is known that occlusion of the coronary sinus increases the coronary sinus pressure to levels greater than the distal coronary artery pressure, thus establishing a gradient for venous flow from the coronary sinus to the ischemic region when the coronary sinus is being occluded. It is well known that a desaturation of blood in the ligated coronary artery occurs according to a veno-arterial pressure gradient and reversal of flow at the microcirculatory level. Pressure forces within the ischemic vascular bed caused by alternating flow over the ischemic territory also influence perfusion of the ischemic region from nonischemic myocardium and result in delivery of small amounts of oxygen through collaterals and further enhance the removal of toxic metabolites in the deflation interval.[28] Bayer and associates[29] showed that the coronary sinus pressure was an important determinant of desaturation in the occluded artery, supporting the hypothesis that the degree of perfusion achieved with ICSO depends on coronary sinus pressure. Thus because of the pressure gradient,

the blood is squeezed by the healthy myocardium into the relatively empty coronary venous system in the ischemic zone. The sudden release of the coronary sinus occlusion results in a rapid drainage of the excessive volume not only from the well-perfused zones but also from the microvasculature recruited during the balloon occlusion phase, allowing an optimal washout of metabolites.

Zalewski and colleagues[27] reported on the effects of various modalities of myocardial protection devices on the extent of myocardial salvage in an experimental model, with 7 different groups undergoing different protection techniques, including retrograde perfusion and ICSO. They concluded that only arterialization of the cardiac venous system, and not retroperfusion with venous blood or pressure-controlled intermittent occlusion of the great cardiac vein, was capable of reducing the size of the infarction. However, their analysis also revealed higher rates of complications in terms of myocardial hemorrhage in animals undergoing high-flow retroperfusion, which was explained as a consequence of the impaired drainage from the retroperfused region of the myocardium. This potential side effect of retrograde perfusion has also been previously described by other authors.[3,30,31] Furthermore, on the basis of xenon-133 injections in the great cardiac veins of dogs subjected to arterial blood retroperfusion in the presence of left anterior descending coronary artery occlusion, Cohen and coworkers[32] describe that only 10% of the injected isotope actually reaches the myocardium distal to the coronary occlusion site, suggesting that the delivery of oxygenated blood might be insufficient as an additional nutritional support to the ischemic myocardium. Thus the question arises of whether the beneficial effects found in several trials with active retroperfusion might have been related to the high coronary sinus pressures achieved as a result of retroperfusion and therefore were caused by an increase of outflow impedance and not necessarily by the substantial delivery of oxygen into the ischemic bed.

In our meta-analysis we found that although retroperfusion with arterial blood resulted in 10.2% greater salvage than intermittent occlusion of the coronary sinus, this difference was not significant. Although, as stated above, the small sample size does not allow a definite answer, pathophysiologic considerations might imply that an arterial blood source might not be necessary to protect jeopardized myocardium, especially in consideration of the fact that active retroperfusion is associated with higher rates of complications caused by uncontrolled impedance to venous outflow.

Mohl and coworkers[20] describe the use of coronary sinus pressure as an important parameter to optimize occlusion-release cycles of the venous effluence. The coronary artery flow during coronary sinus occlusion is reduced according to the pressure increase in the venous circulation, while the plateau of the systolic pressure increase is reached. This reduction of flow is overpaid by a hyperemic response–like flow increment. Mohl and coworkers[20] have documented that an occlusion of the coronary sinus through inflation of the balloon for 15 $\pm$ 4 seconds generates a plateau in coronary sinus pressure. An inflation time of 10 seconds to obtain this plateau has also been reported previously.[33] In contrast, Feindel and associates[34] describe an occlusion of the coronary sinus for only 5 seconds, which by no means is sufficient to reach a pressure plateau and might thus explain why their experiments revealed no favorable results for ICSO (achieved coronary sinus pressure during coronary sinus occlusion in trials of Feindel and associates[34]: 17.1 $\pm$ 6.4 mm Hg; achieved coronary sinus pressure during coronary sinus occlusion in trials of Mohl and coworkers[20]: 44.0 $\pm$ 7.0 mm Hg). This is about the same pressure Feindel and associates[34] reached in their retroperfusion studies resulting in significant salvage. In contrast, Aldea and colleagues,[13] who achieved about the same coronary sinus pressure with both methods, also reported similar salvage in both groups. The smaller amount of salvage in some of the ICSO studies therefore might be explained by the insufficient filling of the coronary venous system to allow redistribution of blood in significant quantities from the nonischemic myocardium to the ischemic zone, thus preventing an optimal recruitment of collaterals.

The negative association between remaining infarct size and the achieved coronary sinus pressure in the ICSO group suggest the potential of the transient pressurization of the venous compartment in inducing myocardial salvage, although results have to be interpreted with caution because of the lack of raw data. Furthermore, the results of the negative correlation between achieved coronary sinus pressure and myocardial salvage during the addition of active retroperfusion can be interpreted as a potential hazard of this method. This can be seen also in the relationship to the amount of retroperfusate.

The seeming contradiction of the relationship between pressure and salvage potential comes as a surprise only at a first glance because the pressure in the ICSO group is only the consequence of myocardial contraction on the venous compartment during coronary sinus occlusion, whereas the pressure observed in the ICSO plus retroperfusion group is the consequence of summing the intramyocardial pressure acting on the venous compartment and the external pumping force of the retroperfusate. It is therefore no surprise that the potential hazard of myocardial hemorrhage can be seen in active retroperfusion.[27] It seems that 2 factors act in opposition: first, the ability of the pressure increase to induce myocardial salvage, and second, the improper timing of outflow impedance leading to the engorgement of the coronary microcirculation, thus reducing positive results by inducing severe changes of coronary artery flow, myocar-

dial hemorrhage, edema formation, and subsequent decrease of myocardial performance.

Our own experience with coronary sinus interventions in a clinical setting applying PICSO during the early reperfusion period showed improvements also in regional myocardial function.[35] PICSO was applied in 15 patients with 3-vessel disease undergoing on-pump coronary artery bypass grafting for about 60 minutes during the reperfusion period, and the results were compared with those of 15 control subjects. A significant improvement of regional function in hypokinetic segments ($P < .04$ treated vs control subjects) was found. In addition, severely hypokinetic segments significantly improved during PICSO therapy from prebypass values ($P < .01$), whereas in control subjects these changes were not significant. With this relatively simple method using a balloon catheter in the coronary sinus without additional blood supply, one can expect a reduction in myocardial jeopardy during beating-heart surgery.

In conclusion, this meta-analysis demonstrates that myocardial protection through the coronary sinus has an efficacy in reducing the size of experimental myocardial infarction irrespective of the time of ischemia and subsequent revascularization procedures. Active retroperfusion, with its known difficulties, resulted in an insignificant further reduction of the experimental infarct size in comparison with intermittent occlusion of the coronary sinus alone. In addition, these results show the importance of a physiologic adaptation of the coronary venous pressure increase, as well as the amount of the retroperfusate, to optimize the salvage potential and to minimize the consequences of the potential hazard of myocardial engorgement.

Evaluation of the effects on transient ventricularization of the venous vasculature as a consequence of all known coronary sinus interventions seems to be the logical next step to improve our understanding on the salvage potential of these methods.

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