1. Introduction

In recent years, the demographics of patients admitted for coronary interventions and revascularization procedures have changed, and there is an increasing need for complex high-risk interventional procedures (CHIP). Despite the development of sophisticated reperfusion strategies and the availability of logistic treatment networks for acute coronary syndromes (ACS), the management of obstructed myocardial microcirculation and subsequent myocardial deterioration remains challenging. Furthermore, there are large variations in reperfusion treatment across Europe; a substantial number of ST-elevation myocardial infarction (STEMI) patients in Eastern and Southern Europe are not receiving any reperfusion therapy [1]. Although mortality from acute events has decreased, therapies to prevent or attenuate postinfarction left ventricular remodeling have changed little, leaving an increasing cohort of patients at risk of severe heart failure [2]. Current routine therapies in ACS focus on the ischemic/reperfused microcirculation and on structural regeneration. Despite timely reperfusion, molecular,
biochemical and immunological changes of the former deprived microcirculation persist, as well as areas of structural obstruction, particularly in the post capillary venules. Therefore there is a need for methods to further reduce microcirculatory obstruction, an important prognostic factor for morbidity, mortality and quality of life [3,4]. In addition to restoring the microcirculation, cardioprotection and structural regeneration remain important in the treatment of ACS.

This article will discuss effective therapies and feasible catheter interventions using the back door of the heart for myocardial protection before, during and after the ischemic insult, particularly in the early reperfusion period.

2. The origin of coronary sinus interventions

The coronary venous route to access deprived myocardium and thus the obstructed microcirculation has a long history, beginning with retroperfusion of arterial blood in the late 19th century and progressing to the development of pressure-controlled intermittent coronary sinus occlusion (PICSO) in the 1980s (Fig. 1) [5–7]. Although there is little doubt that cardiac veins are useful access routes to jeopardized myocardium, few concepts have progressed to clinical development. The coevolution of interventional cardiology and cardiac surgery hindered widespread applications of coronary sinus interventions (CSI). However, the recent availability of novel interventional technologies has reversed this trend and revived interest in CSI.

The concept of PICSO, which uses the coronary sinus pressure for termination of obstructing venous flow in contrast to fixed timed ICSo, has recently been further developed using new technology. There are abundant data on myocardial salvage in experimental ischemia as well as in patients with lysis therapy during or following ischemia as well as reperfusion [8,9]. Clinical data also support the use of PICSO in patients after global ischemia and in heart failure patients [6,10,11]. Recently presented data detail the application of PICSO during primary PCI in the early reperfusion period [12,13].

The primary aim of coronary sinus interventions was retroperfusion of arterial blood to the myocardium, but preclinical and clinical data have suggested other beneficial effects, primarily redistribution of flow towards underperfused zones and subsequent washout as well as offering the potential to revive regenerative pathways, ultimately restoring structural integrity. The first clinical application of the concept of using the coronary sinus to access ischemic myocardium was in the 1940s [14]. A series of pathophysiological studies enhanced understanding of the reaction to elevated pressure in cardiac veins as well as reflexes originating from the endocardium close to the orifice of the coronary sinus [15,16]. Further studies showed the effects of coronary sinus occlusion techniques on the behavior of the coronary microcirculation [17]. Corday and Meerbaum [18,19] developed interventional retroperfusion methods such as synchronized retroperfusion (SRP) and applied them clinically, forcing arterial blood retrograde via a catheter system during diastole into the ischemic microcirculation (see video 1) [20]. Further research was halted following a combination of ambivalent results, unstable technology and the development of alternatives. Boekstegers refined the retroperfusion technology using a selective perfusion technique with subsequent suction that showed positive results in the clinical setting [21,22]. Meerbaum achieved retrograde lysis of coronary artery thrombus by coronary venous streptokinase administration [23]. In early clinical studies, PicSO (pressure observed intermittent coronary sinus occlusion without automatic closed loop, but observer control of pressure increase) was also able to enhance clot lysis significantly, even when given intravenously (p < 0.05) as compared to controls (Fig. 2) [8]. In addition, retroinfusion has been employed in stem cell research and gene therapy, showing favorable results when compared to other delivery routes [24,25].

3. The importance of pressure control during coronary sinus occlusion

Coronary sinus occlusion (CSO) techniques such as ICSo/PICSO and the Banai stent [26] are based on changes in the pressure and flow relations in the normal and ischemic heart. During coronary sinus occlusion, redistribution of flow within the venous compartment allows access to deprived perfusion zones. During temporal occlusion as seen in ICSo/PICSo procedures, a phase of washout follows the filling of the venous compartment (see videos 2 and 3). In contrast, the Banai stent results in a chronic elevation of coronary venous pressure and may lead to severe side effects on coronary circulation including restrictions in venous flow and permanent reorganization of the venous outflow pattern [27,28].

During ICSo, the temporary occlusion of the coronary sinus (which collects about 70% of the myocardial outflow) induces a redistribution of venous blood and plasma-dense fluid from normally perfused territories into underperfused areas, such as severe atherosclerotic coronary arteries and in ACS with additional thrombus burden. The temporary increase of venous pressure in the coronary sinus induces a continuous rise and fall of pressure gradients in the microcirculatory bed, clearing debris and eliminating metabolic waste (Fig. 3) [6,29]. Reactive buffer systems and the action of osmotic, ionic and, most importantly, mechanical forces squeezing blood into the occluded microcirculation, reduce the area of the no reflow zones. Coronary sinus occlusion pressure reaches a systolic plateau resulting from the squeezing action of myocardial contraction. Since redistributed blood flow needs time to fill the venous compartment, these systolic pressure peaks rise constantly, reaching a plateau after several seconds. During PICSo and PICSo, this plateau level signals the reopening of venous drainage and enables optimal redistribution of venous blood (Figs. 4, 5). The pressure in the occluded coronary artery fluctuates according to the pressure in the coronary sinus, and the arterial pressure decreases during coronary sinus release.

Several CSI techniques have undergone investigation. Animal research by Lazar et al. showed that PICSO was superior to IABP and that a combination of both methods enhanced the anti-ischemic effect during urgent surgical revascularization [30–32]. The antiarrhythmic effects of pICSO have also been observed in animals [33]. More recently, the historic concepts of ICSo and PICSo have been replaced by PICSo [11].

Currently the applications of PICSo have focused on ACS. In an experimental animal study, Jacobs et al. found that PICSO performed during reperfusion significantly enhanced myocardial salvage and postulated that PICSO may decrease heart rate by a reflex mechanism that is mediated by vagal afferents [34]. A clinical study, the Prepare RAMSES trial (reperfusion after acute PCI in myocardial infarction and coronary syndromes: efficacy and clinical significance), which aimed to further analyze the salvage potential of this method, has recently been completed. This study followed the first-in-man study using new technology [12]. Prepare PICSo included 15 patients with stable angina scheduled for PCI of the left anterior descending artery (LAD). Balloon occlusion of the LAD was performed twice, once with and once without PICSo and lasting maximally 3 minutes each, to document the effect of PICSo on coronary sinus pressure and LAD wedge pressure. PICSo resulted in a marked increase in coronary sinus pressure with no device-related adverse events reported [11]. In a recently presented study of 32 heart failure patients undergoing resynchronization therapy, PICSo was performed on 8 patients for 20 minutes versus 24 controls. At 5 year follow-up, the metabolic, biochemical and molecular changes induced indicated that PICSo has regenerative potential beyond its acute effect on myocardial ischaemia [35].

In order to realize the full potential of this intervention, questions remain regarding the application of PICSo in ACS. There is also need for additional data to optimize the time window of PICSo to prevent/reverse reperfusion injury, to explore the potential to treat different ischemic perfusion territories and reduce the volume of obstructed microcirculation. Although early and recent clinical results are
Fig. 1. Historical overview of coronary sinus interventions.
promising, there is also a need for long-term data from a propensity-matched trial to establish clinical significance.

However, there are major limitations associated with analyzing myocardial salvage in PICSO. It is known that PICSO interferes with edema formation and increases the energy in border zones by vasodilatation of the microcirculation [33,36,37]. These findings demonstrate a reduction in the perfusion deficit and therefore reduce the evidence measured by magnetic resonance imaging (MRI), since it detects edema, which is claimed to be washed out, and positively influenced by PICSO. Myocardial salvage is assessed by MRI several days after the acute event and therefore includes PICSO effects on the area at risk, since deprived perfusion zones are normally measured experimentally before therapy starts. Therefore MRI data in PICSO research might blunt positive PICSO effects, reducing the perfusion deficit and enhancing washout. These effects of PICSO should be taken into account since recent data emphasize the importance and prognostic values of early changes in ischemic/reperfused microcirculation [38,39].

Stoller and colleagues reported that the reduction of ischemia in patients treated with brief ICSO periods depends on collateral flow [10]. Variable levels of effectiveness of ICSO have been observed and seem to be dependent on the location of the balloon within the coronary sinus and therefore the amount of redistributed blood as well as the optimization of the pressure increase and cycling. A 2004 study on a sheep model showed that optimal timing significantly improves the effectiveness of the method [40]. However, the fixed timings in ICSO occlusion/release cycle pattern prohibit optimal redistribution of blood, a limitation that has been demonstrated in several studies (see also Figs. 5, 6) [41–43].

Inadequate duration of the coronary sinus occlusion release leads to an insufficient retroperfusion/drainage of the coronary sinus and hence decreases coronary artery inflow rather than resulting in washout and hyperemic response (Fig. 5). The unadjusted fixed ICSO approach is unable to correct according to changes in CSP dynamics. Therefore an automatic closed loop method adapting to the dynamics of individuals was developed [44–50]. In the majority of studies, pressure control was achieved by continuous observation and immediate, but observer controlled adjustment of pressure dynamics by the investigator (pICSO). A closed loop system for coronary sinus occlusion has been established that optimizes the beneficial effects of PICSO [51]. The PICSO cycle adapts instantly (beat to beat) according to the physiologic state of the heart. Several parameters must be optimized in a PICSO intervention. In order to ensure sufficient coronary drainage, the release phase must be long enough to allow the next occlusion phase to be triggered by the end of the peak of hyperemic coronary arterial flow, which can be detected by observing venous flow (see Fig. 5). In addition, the occlusion phase must be set to ensure that the systolic coronary sinus pressure reaches a pressure plateau [51]. Further developments have led to the implementation of proprietary algorithms used in the PICSO® Impulse System (Miracor Medical). These calculate the time of occlusion of the venous drainage via the coronary sinus versus the

![Fig. 2. Timeline from symptom onset to reperfusion. The application of about 1 hour of PICSO resulted in a significant shorter lysis time indicating better washout of the obstructed microcirculation. Time points: Onset of pain; Ad admission in the hospital, CL admission in the Cath Lab, at the time of PICSO start the lytic agent was given [reprinted from 8,9].](image-url)

![Fig. 3. Thermograms of coronary artery ligation in a canine model of acute ischemia.](image-url)

time of release of the balloon occlusion according to the coronary sinus pressure dynamics sensed over the fluid-filled line of the catheter.

Variations in coronary sinus dynamics can also be used as diagnostic parameters [50]. Fig. 6 shows CSP dynamics as well as the rapid pressure increase following the opening of the coronary artery is opened in an ovine model [29]. This was corroborated in a clinical evaluation of pICSO during the early reperfusion period. As soon as the bypass grafts were opened, the rise time in CSP shortened and systolic pressure increased significantly, thus reflecting surplus of myocardial inflow [29]. This shows the importance of immediate response to the occlusion/release cycles during pICSO.

4. Optimization of pICSO therapy

In order to optimize pICSO therapy, the position of the occluding balloon redirecting blood in relation to side branches of the coronary sinus is of outmost importance. Exact positioning in an optimal region of the coronary sinus not only requires expertise, but is also a prerequisite of the effectiveness of the pICSO procedure. The easiest way to access the coronary sinus is the left jugular, subclavian or brachial vein. Since a routine anticoagulation regimen is used in ACS and to minimize the risk of bleeding, central venous punctures are avoided in several centers endorsing peripheral veins. The femoral approach has been extensively used and results in favorable catheterization times [11]. The balloon catheter is positioned into the so-called “silent zone” of the coronary sinus (see video 4). Infrequently, an obstructing valve at the coronary sinus orifice hampers the positioning of the catheter within the silent zone of the great cardiac vein.

It is also important to stabilize the catheter system against the force of the outflowing blood, especially during the hyperemic response increasing the venous velocity (Fig. 7A, B). The pressure within the pneumatic balloon catheter is monitored, avoiding any excessive force on the vessel wall and allowing maximal safety. Since the orifice of the coronary sinus is covered by endocardium and contains nerve endings, reflexes such as hypotension and bradycardia have been observed in animals [15,16]. The squeezing action of the heart creates the pressure

![Fig. 4. Schematic of coronary venous flow redistribution in deprived perfusion zones by pICSO. Note that collateral flow from uncompromised coronaries facilitated by vasodilatation of vasoactive molecules produced by pICSO enters the border zones and improve perfusion as well as metabolism in these areas. There is a concomitant increase of the coronary sinus pressure, reaching a systolic plateau after a few seconds, and with a delay the postocclusive arterial pressure shows a synchronous increase. Diastolic pressures also increase according to the volume increase in the coronary sinus.](image)

![Fig. 5. Mean arterial inflow (CXF) and great cardiac vein flow (GCV) in relation to coronary sinus pressure during CS occlusion. Note the hyperemic venous flow indicates a surplus of washout. The negative flow during occlusion depicts retroperfusion. Note that pressure control in the coronary sinus is necessary to prevent permanent coronary inflow reduction. With pressure control mean coronary flow remains unchanged due to the “hyperemic response” during coronary sinus occlusion release [reprinted from Mohl et al., 2005 40].](image)
increase and forces the blood backwards into deprived zones; it is therefore important to collect as much inflow as possible from veins draining into the occluded section of the coronary sinus. The rate of rise gives an estimate of the capacity to be filled by retroperfused blood and is a summation of the venous compartment and the coronary microcirculation deprived from normal circulation. Epicardial blood flow into the deprived coronary vasculature and subsequent washout during the release phase therefore reduces the so-called ‘no reflow’ zones that are present in patients with ACS and allows a shift of blood towards the endocardium (Fig. 4).

5. The salvage potential of PICSO

The significance of myocardial salvage by ICSO has been established in a meta-analysis of 7 experimental trials comprising 125 test animals that showed an inverse relationship between achieved (developed) coronary sinus systolic pressure, (i.e. occlusion duration and elevation of the coronary venous systolic pressure per minute multiplied by the application times of ICSO) and infarct size [52]. The so-called “dose dependence” between optimized ICSO therapy and salvage has been documented in different species and different durations of ischemia [52].

Syeda et al. reported a significant reduction in infarct size of 29.3% in the pICSO group compared to the control group (p < 0.001; 95% confidence interval, −40.9 to −17.7), which correlated to the achieved (developed) coronary sinus pressure increase per minute (r = −0.92; p < 0.007) [52]. This dose-dependency has been recently confirmed by the Prepare RAMSES study, which showed a significant correlation (r = 0.70, p = 0.008) in reduction in infarct size and the cumulated coronary sinus pressure modulation over time [53]. This has led to the development of an algorithm by Miracor Medical Systems that automatically calculates the PICSO quantity applied. The quantity is calculated as:

\[
PICSQO \; Quantity \; = \; \sum_{n=1}^{\text{Total ICSO Cycles}} \left( (sCSPP_n - dCSPP_n) \times (sCSPP_n - CSPDA_n) \times \text{IHT}_n \right)
\]

(Balloon inflation hold time) \times (mean systolic coronary sinus pressure plateau – mean coronary sinus pressure during deflation) \times (mean systolic coronary sinus pressure plateau – mean diastolic coronary sinus pressure plateau), summed over the complete PICSO procedure and expressed in [mm Hg]. It therefore reflects the magnitude of coronary sinus pressure modulation during the complete PICSO procedure.

The meta-analysis by Syeda et al. analyzing different experimental ischemia protocols showed that additional retroperfusion of arterial blood during ISCO was found to increase salvage by around 10%, but dose dependence data showed that the amount of blood retroperfused had an inverse correlation to salvage (r = −0.97; p < 0.004), indicating a counterproductive engorgement of the coronary vasculature. Therefore, redistribution of venous flow together with periodic washout of metabolites, rather than additional arterial infusion and perfusion, is responsible for myocardial salvage [50,54,55].

The relationship between the hemodynamic force of periodic elevation of coronary venous pressure on jeopardized myocardium and salvage has only recently been appreciated because historically, the scientific mainstream associated beneficial effects of CSI and myocardial salvage with delivery of oxygenated blood. Salavage never occurs in Krog’s-like diffusion cylinders around major “arterialized” retroperfused cardiac veins, but rather in border zones of deprived myocardium, therefore it is very unlikely that retroperfused oxygen is the benefactor in CSI. On the contrary, it is currently believed that redistribution of venous blood into the center of ischemia and washout, thus maintaining basal metabolism as well as vasodilation, collateral flow and improved perfusion of the border zone leading to increased energy storage is the main factor of salvage in CSI (see videos 5,6) [37,56].

Clinical data on myocardial salvage and pICSO are limited to applications combined with lysis therapy and date back to the early clinical trials of CSI [7]. However, long term clinical trial data are available, which should be corroborated during reperfusion by PPCI in current clinical trials [9]. Although these historical studies have employed primitive technology and observer limited pICSO, clinical experience has
supported the findings of animal studies [8,9]. Enzymatic infarct measurements in patients with a lysis protocol with and without PICSO showed significantly less total creatine kinase (CK) release than that of the control group, an important finding since CK is a prognostic indicator following acute myocardial infarction (MI) [57]. Infarct size assessed at 30 days after onset of symptoms was significantly smaller for the PICSO group compared with the control group [9]. Although CS catheter placement required additional treatment time (mean time to insert a balloon catheter into the CS was 11 ± 4 min) the period to the completion of reperfusion in the infarct-related artery from the initial administration of thrombolysis agents was significantly shorter for the PICSO group (28 ± 12 min) than for the control group (41 ± 18 min, p = 0.014) (Fig. 2). The reduced procedure time in the PICSO group resulted from enhanced clearing of the microcirculation and even the site of coronary occlusion from thrombus (as seen by Meerbaum in animal models [23]). A left ventriculogram at 30 days after MI showed that the PICSO group had significantly smaller abnormally contracting segments (21.4 ± 16.5%) than the control group (31.9 ± 10.6%; p < 0.05). The global ejection fraction, however, did not differ significantly among groups.

Surprisingly, 5-year follow up showed results on risk reduction to suffer from re-infarction or major cardiac events: 96% risk reduction for re-infarction (95% CI: 61%–99%), 86% risk reduction for major adverse cardiac events (MACE) (95% CI: 48%–96%) after PICSO. Freedom from major adverse cardiac events was 82% for the PICSO group but only 23% for the control group (Fig. 8A, B). These results are noteworthy since they show superiority even against recent analysis of STEMI by Pedersen et al. [58] even after risk adjustments for differences in times to reperfusion and correcting for residual stenosis in the culprit vessel after 30 days. In context with Weigel's findings on upregulation of vasoactive and cardioprotective molecules in experimental studies applying PICSO and recent clinical findings by Kusmic supporting the clinical effectiveness of upregulation of HO-hemeoxygenase, PICSO unfolds a second important mechanism, namely support of regenerative efforts of the myocardium in jeopardy [37,59]. These discoveries have been a turning point in the knowledge of the basic mechanism of PICSO and have led to the development of the hypothesis "embryonic recall", claiming that PICSO interferes with molecular cascades during infarct healing and might initiate structural recovery beyond salvage.

Historical data for PICSO in ACS are only available for intervention in the late ischemic time, but before reperfusion. Recent advances enable intervention in the early reperfusion period. It may be possible to commence PICSO when passing the guide wire to re-open the coronary occlusion before treating the residual stenosis. Furthermore, the existing relationship between cellular damage and enzyme leakage during PICSO and intensified washout relates to better preservation of regional function [29].

Recently van de Hoef et al. compared matched controls with 30 patients with acute coronary syndromes treated with PPCI and additional 90 minutes of PICSO in the reperfusion period. He confirmed additional salvage (baseline versus 4 months) in the PICSO group compared to matched controls measured by MRI (41.6 + /– 8.2% vs. 27.7 + /– 9.9% p < 0.04) [53].

6. Molecular basis of structural regeneration by PICSO

Supported by the paradigm change mentioned above, PICSO can be envisioned as the combination of two independent mechanisms: access to deprived myocardium by clearing the obstructed microcirculation and its regenerative potential (Fig. 9). In order to understand the regenerative process, it is necessary to revisit historic data. A report of the Beck's procedure (permanent occlusion of the venous outflow with subsequent arterIALIZATION of the venous coronary vascular compartment) on long-term histologic changes of ischemic myocardium described many vascular channels distal to the occluded artery [60], which indicates neoangiogenesis. It has been suggested that pulsatile pressure might be the origin of these changes [61], leading to the "embryonic recall" hypothesis, formulated to elucidate the mode of action of PICSO [62].

The "embryonic recall" hypothesis postulates that PICSO directly interferes with the healing process after MI and the development of neoangiogenesis in the myocardial infarct zone. Under normal circumstances, the contribution of neoangiogenesis to the infarct bed capillary network is insufficient to enable the tissue growth required for contractile compensation, but PICSO (by its mechanotransduction effect) initiates developmental processes in the adult heart. During cardiac development, molecular signals are needed to induce structural maturation. The first cardiac pulsations in the primitive heart tube are sensed via endocardial cells and as a result, molecular pulses initiate structural development of the myocardium in the embryo. In this hypothesis, PICSO initiates the same molecular pulses in the adult myocardium leading to regeneration.

The reopening of an epigenetic window into the morphogenetic pathways of the developing heart for cell survival, including pathways such as mechanotransduction and activation of endothelium, is well established [63]. Since it has been suggested that mechanical factors
play a major role in coronary angiogenesis as well as sculpturing the developing heart, a biomechanical intervention should affect myocardial gene expression. It has been shown that shear stress on the endothelium during ischemia induces signaling pathways, leading to the formation of collaterals via pressure and flow gradients within the microcirculation and consequently to increased shear stress. Periodic venous pressure elevation by PICSO therefore results in known effects of retroperfusion such as myocardial salvage, as well as having angiogenic effects. The upregulation of vasoactive (adenosine, vascular endothelial growth factor [VEGF] and its receptor) as well as cardioprotective (heme oxygenase [HO]) molecules has been observed in animal studies, supporting this hypothesis [37, 56-65].

The molecular cascade induced by the mechanical force on endothelium has been studied on two functionally interrelated, proangiogenic genes in porcine myocardium: HO-1, an anti-atherosclerotic molecule also known to be involved in vasodilation, and VEGF, which has shown recently to be an important support leading to better cardiac function in 4 week follow up after experimental infarction [59, 66]. It is anticipated that the microcirculatory stretch induced by PICSO is associated with the upregulation of HO-1 and VEGF mRNA, two markers expressed by the activated endothelium, whereas the ischemic pathway via hypoxia-induced factor (HIF) activity remains unchanged [67]. This upregulation of pro-angiogenic molecules have been observed in remote zones as well as in border zones and also to some extent in ischemic zones. It is noteworthy that that VEGF/VEGF2 and their receptor proteins were markedly upregulated in myocardial cells in the remote zone but not in the coronary sinus blood during experimental coronary artery occlusion in pigs [35, 65-66, 68-72]. These are significant findings, since soluble VEGF in peripheral blood may be a prognostic indicator for restenosis after stenting [70].

7. Future developments

Although PICSO might be best applied immediately before PPCI, there remains a need to investigate the effects of a longer time window of PICSO application in the early reperfusion period. Reperfused myocardium with cell death, (i.e. apoptosis and necrosis) cell signaling and cell migration is a potential analogue to a lizard's blastema formation combining growth signals with dedifferentiation of cells inducing structural rescue, which cannot be established in mammalian hearts without additional regenerative phenomena. Many species able to regenerate in adulthood use a blastema, which is an epigenetically controlled regeneration zone combining molecular signals from dying and dedifferentiated as well as migrated cells able to reenter the cell cycle producing structural recovery. It may be expected that coronary sinus interventions produce similar effects. Based on our hypothesis and experimental and early clinical findings, there is a strong rationale for investigating the potential of PICSO in heart failure patients. Future clinical research is mandatory to decipher the regenerative potential of PICSO and to further support the hypothesis that a relatively easy coronary sinus intervention can induce structural regeneration.

8. Conclusion

Clearing microvascular obstruction via cardiac veins has undergone a resurgence in interest in treating patients with complex high risk interventional procedures as well as in ACS. Tables 1 and 2 highlight the most important facts in coronary sinus research including experimental and clinical evidence. Conceptualized decades ago, access to deprived myocardium has demonstrated benefits during ischemia, which have been corroborated by preliminary studies in the era of PPCI. Clinical results indicated that the salvage potential of PICSO is dose dependent, but that a second threshold dependent effect influencing structural regeneration also influences patient outcome. Activation of venous

---

**Table 1**

<table>
<thead>
<tr>
<th>Embryonic recall molecules and their references involved both in development and also upregulated in regeneration as well as through PICSO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecules upregulated during development</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>VEGF, FGFs [71]</td>
</tr>
<tr>
<td>KLF2 [72]</td>
</tr>
<tr>
<td>IL-6 [73]</td>
</tr>
</tbody>
</table>
endothelium by the hemodynamic force of venous blood initiates molecular cascades similar to developmental processes, leading to the possibility that limiting ischemic jeopardy and regaining structural integrity might be a realistic goal for the interventional cardiologist.

### Funding

The project has been funded by the Society of Coronary Sinus interventions. Many of the references are cited here, but also an abundance of more information on coronary sinus interventions is available via the web: [http://www.coronarysinus.com/](http://www.coronarysinus.com/).

Funding was also provided by Jubiläumsfond der Österreichischen Nationalbank AP14128ONB/KP14128ONB.

### Conflict of interests

WM is the inventor of PICSO founder & shareholder of Miracor Medical Systems [www.miracormedical.com](http://www.miracormedical.com).

---

Table 2

Concepts of CSI and studies on pICSO/PICSO on myocardial salvage and regeneration.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Major findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different concepts of coronary sinus interventions</td>
<td></td>
<td>[5,7,14,19,21,22,24-26,75]</td>
</tr>
<tr>
<td>1. Arterialisation of the coronary sinus (Beck’s procedure)</td>
<td>Claims &amp; findings: Improved function in diffuse coronary artery disease, early findings in angiogenesis, improved survival. Many of these procedures have been applied pre CABG and interventional cardiology era.</td>
<td></td>
</tr>
<tr>
<td>2. Synchronized retroperfusion techniques</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Pressure controlled Intermittent coronary sinus occlusion techniques</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Retroinfusion techniques including retrograde cardioplegia</td>
<td><em>Presently used concepts:</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. PICSO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Banai stent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Retrograde cardioplegia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Retroinfusion (gene delivery)</td>
<td></td>
</tr>
<tr>
<td>Mode of action of PICSO</td>
<td>1. Salvage potential</td>
<td>[33,56,75,76]</td>
</tr>
<tr>
<td></td>
<td>1. Redistribution of flow towards ischemic areas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Washout of toxic metabolits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Reducing no-reflow areas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Reopening microcirculation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Improved flow in border zones</td>
<td></td>
</tr>
<tr>
<td>pICSPreclinical studies on myocardial salvage and functional improvement</td>
<td>2. Regenerative potential</td>
<td>[61,62]</td>
</tr>
<tr>
<td></td>
<td>1. Different species and forms of myocardial ischemia and reperfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Jacobs performed the only equivalent study on PICSO and reperfusion to modern PPCI in dogs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Functional studies CAD in dogs and PICSO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Comparison of pICSO with IABP and LVAD</td>
<td></td>
</tr>
<tr>
<td>Preclinical studies proposing structural regeneration</td>
<td>Study in swine and coronary artery occlusion</td>
<td>[37,56,64]</td>
</tr>
<tr>
<td></td>
<td>Increase in angiogenetic and vasoactive molecules (Ho-hemoxygenase, VEGF, Adenosine) supporting the claim perfusion increase and increase in high energy phosphates in ischemic borderzones</td>
<td></td>
</tr>
<tr>
<td>First in man</td>
<td>Randomized study of pICSO during the early reperfusion period in CABG (15 pICSO vs. 15 controls)</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>Functional improvement of severely depressed regional function, trend towards clinical improvements (less infection, shorter ICU stay, less catecholamine support)</td>
<td></td>
</tr>
<tr>
<td>Randomized clinical study on pICSO in ACS and lysis therapy</td>
<td>15 pICSO vs. 15 controls during lysis</td>
<td>[8]</td>
</tr>
<tr>
<td></td>
<td>30% increase of salvage Earlier clot lysis (see Fig. 2)</td>
<td></td>
</tr>
<tr>
<td>Long-term follow up of study above</td>
<td>5 year follow up of Komamura’s study cited above</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td>Significant reduction of MACE and re-infarction (see Fig. 8A, B)</td>
<td></td>
</tr>
<tr>
<td>pICSO in heart failure</td>
<td>8 patients with 20 minutes PICSO during resynchronization therapy vs. 24 controls</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>No changes in short term hemodynamics and metabolism</td>
<td></td>
</tr>
<tr>
<td>Long term follow up pICSO in heart failure</td>
<td>ATOS I study retrospective controlled trial in heart failure patients</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>Reduction of mortality Molecular insight in mode of action of PICSO (hypothesis of embryonic recall) see figure</td>
<td></td>
</tr>
<tr>
<td>New generation of PICSO technology</td>
<td>1. Prepare PICSO</td>
<td>[12,13]</td>
</tr>
<tr>
<td></td>
<td>2. Prepare Ramses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Increase in postocclusive coronary artery pressure trend towards reduction of ST segment elevation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Dose dependent (CSP quantity) trend towards decrease of infarct size</td>
<td></td>
</tr>
</tbody>
</table>
Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.carrev.2014.12.004.

References


Tomanek RJ, Christensen LP, Simons M, et al. Embryonic coronary vasculogenesis and angiogenesis are regulated by interactions between multiple FGFs and VEGF and are influenced by mesenchymal stem cells. Dev Dyn 2010;239:3182–91.


