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I would like to share with you the PICSO concept salvaging jeopardized myocardium using coronary venous hemodynamics.

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These are my disclosures all data have been published in peer reviewed journals. Originals can be sent to you upon request via email

I have a relationship with Miracor and I received an educational and travel support by St. Jude medical

3)

Time is muscle and early revascularization is key in acute coronary syndromes. What is less appreciated however is that necrosis persists and reperfusion injury, inflammation, apoptosis, and matrix degeneration continues leading to early and late remodeling with the potential of infarct size expansion and the development of heart failure.

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So it is no surprise that even the continuing improvement of mortality rates in myocardial infarction are counteracted by increased morbidity and late heart failure deaths.

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Several concepts have been tried experimentally and clinically from Adenosine delivery to shock waves, pre and post as well as remote conditioning.

We have developed the PICSO concept short for pressure controlled intermittent coronary sinus occlusion, a method priming the target tissue towards regeneration. It is intended in acute but also chronic ischemia.

This intervention uses a periodic balloon blockade of the venous drainage and the systolic pressure rise (which is the primary mode of action of this therapy) controls the redistribution of venous flow towards ischemic areas.

6)

Access to underperfused myocardium and in situ activation of the pluripotent venous endothelium is achieved inserting a balloon catheter into the coronary sinus. Using this backdoor of the heart has been tried earlier with retrograde arterialization methods with external pumps which showed beneficial effects however inconsistent improvements. The reason of this inconsistency was the unoptimized pressure increase, to our knowledge today however the optimal pressure rise is the primary mode of action of this therapy.

6A) and 6)

PICSO however by periodic occluding the coronary sinus uses only the force of the venous blood and therefore the hemodynamic power of the heart itself.

7)

Today balloon occlusion is facilitated with a closed loop system for physiologic control of redistribution of flow, washout and clearing of the microcirculation therefore modulating inflammation. Activation and the generation of vasoactive molecules induces acute collateralization and metabolic changes.

8)

With each heart beat the coronary venous pressure rises and upon reaching a plateau the blockade is released allowing normal drainage, this is repeated for the period of the therapy.

8A)

Using a flowprobe around the adjacent vein of an occluded artery in an acute experiment you see the reflow into the ischemic zone according to the

pressure rise in the coronary sinus. After release more blood drains this area according to the increment of collateral flow. With this “optimized” procedure coronary artery flow, which would be affected by unphysiologic blockade remains unaffected.

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PICSO is intended for acute coronary syndromes but can also be applied in heart failure in interventions and open heart surgery.

10)

During normal perfusion coronary artery inflow during diastole is followed by systolic coronary venous outflow.

10A)

In presence of coronary artery occlusion a perfusion deficit develops

10B)

And after stenting and acute revascularization normalization of epicardial flow leaves parts the microcirculation compromised.

10C)

Temporal outflow obstructions by PICSO venous flow waves clear the microcirculation and by inducing vasoactive molecules open up collateral flow.

11)

Periodic reversal of flow and washout improves perfusion in borderzones and clears the microcirculation and it activates pluripotent venous endothelium.

12)

The clinical context and the importance of clearing the microcirculation has been shown by a significant difference in survival according to the integrity of the microcirculation with good survival when complete washout is achieved

and compromised outcome when damage leads to thrombosis apoptosis and inflammation.

13)

This means that even after restoration of epicardial flow

13A)

Patchy ischemia thrombosis and constriction of the microvasculature persists

13B)

And as seen here microthrombi can develop. This picture is taken from a blood sample drawn from the coronary sinus from a surgical patient treated with PICSO during the reperfusion period showing such a thrombus washed out.

14)

In analogy to the situation in the embryonic heart where hemodynamics sculpts the developing heart reversal of flow as it exists periodically during PICSO in venous vasculature activates endothelium via shear stress and pulsatile stretch of the cytoskeleton. This results as seen in in vitro studies in the growth of additional cilia detecting reversal of flow.

15)

This leads to the generation of vasoactive neoangiogenic and even antiatherosclerotic molecules ultimately leading to salvage.

16)

We studied the PICSO effect on angiogenic gene expression in a 3 hour permanent occlusion protocol and took tissue samples from remote areas as well as from the ischemic and border zone.

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We found a significant upregulation of VEGF in all zones and also for the anti-atherosclerotic agent Hemoxygenase in the infarct zone.

18)

This was corroborated recently by the finding that VEGF and VEGF receptor 2 protein are expressed in a 3 hours occlusion 1 hour reperfusion model in the endothelium of the microcirculation.

19)

A meta analysis on salvage by PICSO showed a reduction of infarct size by about 30% which is in agreement with data from a clinical study where PICSO was applied during thrombolysis.

20)

In a post hoc analysis of this trial

20A)

we found a significant risk reduction in the treated group even after 60 months post treatment.

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This was in agreement of the event free survival in the treated group.

22)

If these data are analyzed after standardizing the time from onset of pain to actual reperfusion there was a 96% reduction of risk to suffer an reinfarction

and 86% to experience a major adverse event if the patient was treated with PICSO.

22)

So in conclusion one can say that the dynamics of myocardial infarction does not end after primary PCI and that PICSO might interfere with all stages in acute and chronic coronary syndromes.

We are currently investigating whether these favorable findings can be substantiated using modern technology and whether prevention and reversal of reperfusion injury by PICSO has the clinical significance anticipated.

23)

Thanks go to the Team especially Adriana Gittenberger de Groot from the University of Leiden and her team working on VEGF expression in endothelial cells,

23A)

Prof. Komamura who performed the Japanese study and Dr. Kasahara who did the post hoc analysis of this study

23B)

As well as to my young team in Vienna performing recent human application of PICSO.