

Is activation of coronary venous cells the key to cardiac regeneration?

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Received 13 December 2007

Accepted 23 April 2008

Published online

5 August 2008

www.nature.com/clinicalpractice
doi:10.1038/npcardio1298

Myocardial regeneration for endogenous cardioprotection is an attractive treatment option. The mechanisms by which cardiac cell therapy could induce myocardial regeneration and, ultimately, recovery of the failing heart, however, remain an enigma. As the quest for a better understanding of cardiac regeneration continues, we believe alternatives beyond stem cell research should be considered. In this Viewpoint we focus on the potential to use innate mechanisms that are active during cardiac development. These mechanisms lie dormant in the adult, but can be reactivated during adult life. Regression into embryonic or fetal molecular pathways is seen during physiologic adaptation (i.e. cardiac hypertrophy) and in disease processes such as neoplasia and metastasis. Despite obvious potential, recapitulation of 'epigenetic' embryonic pathways as a means for regeneration of the adult failing heart has been neglected until recently.¹

Mechanotransduction is a simple approach that uses hemodynamic force to activate coronary venous vasculature, and is a viable alternative to mainstream research to recover jeopardized myocardium. Pressure-controlled intermittent coronary sinus occlusion (PICSO) is a clinically available coronary sinus intervention with known cardioprotective effects. This technique seems to have the potential to reactivate embryonic pathways through the induction of shear stress and pulsatile stretch of blood flow in the coronary microcirculation. PICSO works by allowing a pressure wave front to enter the ischemic coronary bed by redistribution of blood in the myocardium during intermittent occlusion of the coronary sinus. After the systolic pressure reaches a plateau, the occlusion is released allowing drainage. Concomitant to this elevation in venous pressure is the increase in the arterial pressure in the occluded coronary artery (the increase of collateral flow), which improves perfusion in border zones resulting in a considerable reduction in infarct size. PICSO, with its confirmed cytoprotective effects in the ischemic heart, acts only by manipulating coronary

venous blood flow; retroperfusion of arterial blood—the suggested benefit in other coronary sinus interventions (see Supplementary Figure 1 online)²—does not occur with PICSO. There has been speculation for some time that improvement in collateral flow is an important parameter in the reduction of infarct size by use of PICSO.³ Experimental PICSO studies have demonstrated significant upregulation in vascular endothelial growth factor (VEGF) and hemoxygenase expression,⁴ effects otherwise difficult to achieve without gene or stem cell therapy. The vasodilatory and regenerative effects of these molecules seem to be essential in the salvage of ischemic border zones, as seen in a range of animal models.⁵

As previously mentioned, mechanotransduction and activation of venous endothelium by pulsatile stretch and elevated coronary venous pressure are the suggested initial mechanisms responsible for the benefits observed. In principle, there are several methods available to change blood flow and pressure in the coronary veins. These range from permanent coronary sinus occlusion with and without retroperfusion of arterial blood, and intermittent occlusion techniques, to a throttle effect recently reported by Banai *et al.* who narrowed the coronary sinus causing a permanent but small increase in coronary venous pressure.⁶ As noted earlier, myocardial salvage is probably related to the increase in coronary venous pressure caused by the mechanical action of the ventricular pressure peaks. If the elevation of coronary venous pressure is prolonged and uncontrolled, the beneficial and desired induction of molecular cascades leading to recovery is counteracted by the severe adverse effects associated with permanent impedance changes in the coronary circulation. On the basis of the high mortality seen in the second stage of the Beck II procedure, we know that a permanent reduction of coronary sinus flow is highly critical. An increase in myocardial impedance by excessive lowering of venous flow worsens the overall hemodynamic state inducing bradycardia and hypotension.

A physiologic adaptation of coronary sinus occlusion is, therefore, necessary to avoid changes in nutritive arterial blood flow. Occlusion–release cycles must be calculated and can vary considerably among patients and within individuals depending on time of measurement. Coronary sinus occlusion during PICSO prevents about 70% of venous drainage temporarily; thus, the timing of occlusion–release cycles is an important determinant of the effectiveness of this procedure, and can vary from 7 s versus 2 s, to 20 s versus 3 s. Of note, pressure control to optimize the occlusion–release times is paramount to achieve the best therapy and prevent venous capacity being exceeded, a situation that could impede coronary artery inflow. Coronary pressure dynamics could also have diagnostic implications, as rises in pressure and the developed occluded pressure are related to myocardial force and perfusion.

In order to find an explanation for the observed effects of PICSO we studied mechanotransduction as a phenomenon brought about by the influence of shear stress on endothelial cells,⁷ which has also been demonstrated to have an important role during early heart development. We speculate that the concept of ‘embryonic recall’ provides an alternative link between coronary sinus interventions and regeneration.¹ In our hypothesis, mechanotransduction as an epigenetic sculptor of cardiac organogenesis is related to the induction of self-regulating dormant pathways of regeneration in the adult failing heart. Pulsatile stretch of coronary venous endothelium achieved by intermittent pressure elevation reactivates dormant pathways in the adult heart. This activation is similar to the effects stretch and shear stress have on the endocardium during heart development and maturation. This ‘embryonic recall’ might, therefore, stimulate neovascularisation and structural regeneration. Zheng *et al.* demonstrated that fluid shear stress can upregulate VEGF production in coronary microvascular endothelial cells.⁷ Furthermore, Groenendijk and colleagues found that mechanical action of blood flow can also affect modeling of the developing heart—disturbed blood flow patterns can cause congenital cardiac malformations.⁸ VEGF upregulation and the ‘milking’ action (i.e. mural pressure of the ventricular contraction compresses the coronary circulation and ejects the blood via coronary veins during systole) of coronary sinus occlusion pressure is central to our PICSO

hypothesis. Furthermore, there is evidence that enhanced expression of VEGF also relates to homing of circulating progenitor cells and *in situ* proliferation of resident pluripotent cells.⁹

PICSO might not just be beneficial in the failing heart: this technique could also prevent reperfusion injury.¹⁰ Factors responsible for reperfusion injury include oxygen-based free radicals, altered myocardial metabolism and calcium overloading.¹¹ Endogenous cardio-protective mechanisms induced in response to ischemia to counteract reperfusion include adenosine production and the release of nitric oxide. As it has been suggested that endothelial cells exposed to shear stress may release nitric oxide,¹¹ new therapy options involving mechanical stimuli of the endothelium could provide more patient benefit.

Early clinical investigations have shown benefits of PICSO used during CABG surgery and in patients with acute coronary syndromes,¹² corroborating experimental studies demonstrating the salvage potential for the ischemic myocardium.^{5,13} A recent re-evaluation of previously reported clinical data shows beneficial long-term effects of PICSO in patients with acute coronary syndromes.¹⁴ PICSO as adjunct therapy in patients with acute myocardial infarction and reperfusion can reduce infarct size by 30% ($P < 0.05$), and reduce the incidence of major adverse cardiac events, as seen after 60 months’ follow-up ($P < 0.0001$; see Supplementary Figure 2 online).¹⁴ To our knowledge, this is the first time PICSO has been shown to achieve such myocardial salvage and clinically significant improvement. Interestingly, our recent evaluation demonstrated that restenosis and the subsequent occurrence of cardiac events were prevented by PICSO in patients with acute myocardial infarction enrolled in a randomized trial. We believe these findings support the conclusion that molecular stimuli can be altered from patterns that mediate inflammation to patterns that induce regeneration by changing the micro-environment of the jeopardized myocardium via treatment with PICSO.

Even in the era of acute revascularization procedures for acute coronary syndromes, many patients could benefit from prevention of reperfusion injury, reverse remodeling and cytoprotection. Potential candidates include those on the transplantation waiting list in whom PICSO could be used as bridge to recovery, patients with acute myocardial infarction or

Competing interests

W Mohl declared an association with the following company: Miracor. See the article online for full details of the relationship. The other authors declared no competing interests.

diffuse chronic coronary syndromes, and those undergoing cardiac surgery in whom enhanced myocardial protection could be beneficial. We speculate that this technique could be especially useful in 'no option' patients (i.e. those with ischemic cardiomyopathies and severe heart failure despite optimum medical therapy), inducing new vessel formation and eventual structural recovery. Unlike other methods such as stem cell transplantation that have limited regional effects, PICSO can, in theory, activate most of the pluripotent venous vasculature because the pressure is transmitted into the total venous circulation.

The concept has been proven in early clinical trials and we feel its time for this simple percutaneous method to undergo further evaluation by the scientific community. We believe that the time has come to introduce PICSO to the clinic as a valuable technique for activation of venous endothelium to initiate myocardial recovery—approaching the same clinical targets as gene and cell therapy. This mechanistic approach based on epigenetic phenomena could provide another pathway for attracting and mobilizing cells able to induce regeneration.

We feel that this concept could lead to a major paradigm change in research into cardiac regeneration. With the focus moving from state of the art cellular transplantation towards manipulation of the milieu of the heart to enhance reparative inborn pathways for clinically significant recovery and, thus, an improved quality of life for our patients.

Supplementary information in the form of two figures is available on the *Nature Clinical Practice Cardiovascular Medicine* website.

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