Work in progress report – Assisted circulation

Intermittent pressure elevation of the coronary venous system as a method to protect ischemic myocardium

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Abstract

Beating heart surgery leaves myocardial areas underperfused and rendered ischemic during brief coronary artery occlusions. In a recent meta-analysis in experimental myocardial infarction, intermittent coronary sinus occlusion (ICSO) proved valid to salvage ischemic myocardium by 30%. Moreover, benefit of this effect can be optimised using coronary venous pressure data. The aim of this study was to evaluate optimisation criteria investigating coronary venous flow data during pressure controlled intermittent coronary sinus occlusion (PICSO). PICSO was performed in 12 adult anaesthetised sheep during occlusion of the left anterior descending (LAD). Additional to coronary sinus pressure (CSP) recordings, venous flow was measured in the great cardiac vein (GCV) via continuous wave Doppler sonography.

Experimental studies provide evidence of retrograde flow toward ischemic zone originating from PICSO. Mean antegrade flow, during specific cycle, is significantly higher than the mean retrograde flow \( P<0.007 \). Additionally, differences between various cycles can be considered significant, too \( P<0.05 \). These experimental data support the notion that transient pressure elevation in the coronary venous system recruits collateral flow towards ischemic myocardium. Optimal timing significantly improves the effectiveness of the method. Ease of this intervention makes PICSO capable of protecting myocardial performance during beating heart surgery even without active retroperfusion.

Keywords: Coronary sinus pressure (CSP); Pressure controlled intermittent coronary sinus occlusion (PICSO); Coronary venous pressure elevation; Ischemia; Great cardiac vein flow; Acute collateralisation

1. Introduction

The concept of beating heart coronary artery bypass grafting is convincing, if one considers the hazards following global cardiac arrest. There are, however, several potential problems like positioning of the heart and its hemodynamic consequences, the quality of the anastomosis, injury to the arterial wall using arterial shunts and regional myocardial ischemia. Whereas most of these problems have been addressed, iatrogenic regional ischemia remains underestimated. One simple access to jeopardised myocardium is the coronary sinus route towards deprived myocardium.

Although several concepts of retroperfusion have been proposed, we focus on the concept of intermittent coronary sinus occlusion (ICSO) [1], which has been developed by our group. Even without retroperfusion of arterial blood significant salvage of jeopardised myocardium occurs. A recent meta analysis [2] of available published data on the salvage potential suggests that the amount of venous pressure achieved during coronary sinus occlusion is inversely related to the infarct size in different species tested. This is in agreement with an improvement in RMBF and the endo/epi ratio according to the CSP rise during coronary sinus occlusion (CSO) enhancing coronary collateral blood flow and modifying the redistribution of regional myocardial flow in ischemic regions [3].

Myocardial salvage induced by ICSO during experimental coronary occlusions as well as in early clinical trials are the result of time dependent ICSO and in one clinical trial in patients with acute myocardial infarction, CSP elevation was limited to 50 mmHg [4]. Earlier observations, including clinical results of the Beck’s procedure, showed that prolonged individually unadapted CSO are counteracting positive effects [5].

We therefore developed the concept of pressure controlled intermittent coronary sinus occlusion (PICSO) to optimise the effectiveness of this method and to prevent unphysiologic limitations of myocardial drainage.

The main goal of this study was to determine the quantity of the great cardiac vein flow (GCV) during different occlusion and release periods of the coronary sinus (CS). The length of the occlusion/release phases is one of the main determinants influencing the success of ICSO. Secondly, we determined differences between ICSO and PICSO, in order to optimise coronary blood flow within the ischemic...
area and to reduce potential side effects in arterial inflow, occurring during a strict time regimen.

2. Materials and methods

2.1. Experimental protocol

A CS pressure controlled feedback system was developed to produce ICSO. It consists of a double-lumen balloon catheter and the PICSO device, Fig. 1. Video 1 shows some sequences taken during experimental intervention.

From a series of 12 animals, data from six sheep were analysed. Sheep weighed between 85 and 109 kg. Anaesthesia was introduced with 2% thiopental (1 mg/kg i.v.) and maintained with fentanyl (0.5–0.75 mg/h). The sheep were intubated and ventilated with a mixture of 100% oxygen and 2% isoflurane for approximately 10 min using a volume-regulated respirator. After controlling the blood gases ventilation mixture was adjusted (40% oxygen and 2% isoflurane). The respiratory minute volume was set to 10–13 l/min at a respiratory rate of approximately 20/min. Blood gases and serum electrolytes were analysed at regular intervals. The sheep were given a continuous-drip i.v. infusion of 600 ml/h Ringer’s solution and 20 ml potassium chloride. An ECG was recorded during preparation and throughout the experiment. Body temperature was maintained at 38 °C. The animals were systemically anticoagulated with a heparin sulfate i.v. bolus (10000 IU) before preparation of the great neck vessels. A left thoracotomy was performed and the heart was suspended in a pericardial cradle. The left anterior descending artery was dissected proximal to the first diagonal branch and two One Transonic® flow probe (2 and 3 mm) was placed around the GCV adjacent to the occluded LAD branch and the other one in standard position in the circumflex (CX) artery, in order to measure the flow in vessels via continuous wave Doppler sonography. A double-lumen 7F catheter, with a curved tip (Contract Medical International GmbH), was inserted from the left internal jugular vein and placed in a stable position with the balloon approximately 25 mm inside the CS after ligation of the azygos vein. CSP was measured by the centre lumen of the catheter and recorded continuously.

2.2. Experimental protocol

Before LAD occlusion animals were stabilised for 15 min. Thereafter, the LAD was occluded for 10 min. In the third phase different occlusion and release cycles of the CS were evaluated. During this period, LAD was alternatively occluded for 3 min and then reopened for 3 min during the same cycle. Pump cycles ranged from 5:3 being the shortest cycle (5 s occlusion of the CS and 3 s of release of the CS) up to 12:8 being the longest cycle. Chosen cycles were performed at random during every surgery in order to prove efficiency of the particular cycle during different periods of the surgery. All haemodynamic signals were recorded on a computerised data acquisition system for biological signals. All animal care and handling were performed in accordance with the guidelines specified by the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the local Institutional Animal Care and Use Committee of the Medical University of Vienna. During the entire experiment, the animals were monitored online to avoid any unnecessary suffering and to ensure complete anaesthesia. The experiment was terminated during complete anaesthesia with a high dosage of potassium chloride injection.

2.3. Thermography

We used a commercially available thermo camera (IR Flex Cam Pro, Infrared Solutions) in order to show qualitative temperature changes during infarction, reperfusion and during ICSO.

2.4. Statistics

Data are presented as mean ± SD. Flow measurements between different cycles, retrograde as well as antegrade,
were tested using ANOVA, followed by Tukey’s post hoc test for comparison between all cycles, with a significance level of $P<0.05$.

3. Results

Obstruction of the blood outflow from the coronary veins into the right atrium leads to a pressure increase in the coronary sinus and the coronary veins reaching a systolic plateau after a few heart beats. The rise time differs significantly between different stages of myocardial perfusion and has been reported by Schreiner [6]. During the occlusion phase, blood penetrates regions deprived from regular perfusion as seen in the thermogram from its border zones. After the CS blockade is released the CSP declines rapidly causing increased venous blood drainage enhancing washout of toxic metabolites as well as of interstitial fluid [7].

Measurements of blood flow in the GCV showed retrograde flow during CS occlusion, dependent of the chosen cycle and ranged from $-3.49$ up to $-27.67$ ml/min (Fig. 3b). During this phase blood penetrates the venous microvasculature backwards. During CS release antegrade flow towards the coronary sinus can be detected, ranging from 27.48 up to 51.45 ml/min, depending on the chosen cycle (Fig. 3a). Mean antegrade flow was significantly higher compared to the mean retrograde flow (42.52 ± 8.59 vs. $-11.07 ± 7.17$ ml/min; $P<0.007$). Analysis showed that particular cycles like: 7:3, 10:4, 12:3, supported antegrade flow more than all the other cycles (Fig. 3a).

Mean antegrade flow during 12:3 cycles was 43.23 ± 1.66 ml/min. Increasing the release phase to 4 s resulted in a decrease in mean antegrade flow to 35.61 ± 0.73 ml/min ($P<0.009$). High antegrade venous flow was recorded using cycles such as: 7:3, 10:4, 12:3 and was significantly higher as compared to the cycles such as 6:3 or 8:6 (43.52 ± 8.59 vs. 25.21 ± 12.8 ml/min; $P<0.05$). The same observation could be made in retrograde flow. Cycles like: 12:4, 12:6 were significantly different in retrograde flow compared to 6:3 or 7:3 cycles, Fig. 3b ($-17.31 ± 9.18$ vs. $-7.31 ± 4.78$ ml/min; $P<0.05$).

Timing of the release phase of the CS less than 2 s limits antegrade flow should be avoided. However, release phases longer than 3–4 s are not of benefit either, because during this period CSP has returned to its base level. During a prolonged release most of the stored venous volume is lost for the repetitive occlusion of the CS. Optimal flow data are in agreement with differences in CSP, since systolic pressures of ‘best PICSO’ cycles are much higher than cycles without optimal flow (51.61 ± 9.89 vs. 44.15 ± 10.4 mmHg; $P<0.001$)

Arterial inflow was measured in the CX artery during different CS occlusion/release cycles with and without LAD ligation to determine contra productive increase of inflow impedance and subsequent perfusion deficits. Indeed CX flow showed a decrease during CS occlusion overpaid by a hyperemic response with a maximum in 2–3 s upon release of the CS (Fig. 4a).

Thermographic recordings during LAD occlusion with and without PICSO application indicate an improved epicardial blood flow distribution, as an effect of the PICSO intervention. Increase of the temperature up to 0.4 °C was noticed.
even in the very centre of the perfusion-depressed regions (blue regions). Moreover, there is a significant decrease of the deprived region caused by improved collateral blood flow crossing the borders of perfusion zones (Fig. 2).

4. Discussion

In the present evaluation, we related the coronary sinus pressure dynamics to the perfusion status and different cycles of timed intermittent coronary sinus occlusions. The results show the importance of a physiologic and individual adaptation of the temporary situation of the myocardial perfusion and its hemodynamic consequences of the dynamics of myocardial ischemia (Fig. 4b).

Redistribution of flow as documented by thermography and probably the salvage potential of ICSO and PICSO is closely related to the acute collateralisation of the ischemic border zones (Fig. 2). To understand our hypothesis of the effect of PICSO on collateral perfusion one has to consider the anatomy of the venous vasculature. Epicardial vessels branch perpendicular transmurally, whereas the microcirculation builds circumferential layers. During perfusion deficits the vascular cushion, protecting the microcirculation from squeezing induced by left ventricular pressure, is emptied within a few heartbeats. Accordingly, bulging of the area and regional ischemia occurs. During venous pressure elevation redistribution of venous flow refills the erectile transmural net of veins opening up the microcirculation especially in border zones for collateral circulation. This induces salvage in border zones. This is not the only beneficial effect of PICSO, since others and ourselves have shown improved washout by this procedure [8,9].

Our results underscore the necessity to observe the coronary sinus pressure during CS occlusion and release continuously and to adapt individually. Although a definite answer of a general usable algorithm for a physiologic adaptation of occlusion/release cycling still has to be determined, venous flow has proved valid as an accurate optimisation criterion.

5. Conclusion

Volume shifts within the myocardial vasculature are the most important effect of ICSO and the timing of the intermittent character of CSO defines the effectiveness and the therapeutic range of this method. Physiologic adaptation of ICSO is necessary. To our present knowledge exact and dynamic feedback to pressures are necessary to avoid adverse effects and to maximise myocardial protection. Our current PICSO system is capable of fulfilling all these requirements.

5.1. Clinical implications

To date two clinical reports on PICSO are available. Our own group has shown an improvement of regional myocardial function in CABG patients. Komamura has shown the efficacy of ICSO in patients with acute myocardial infarction [4,10]. Although these reports were published some time ago, the necessity to protect the heart during acute coronary syndromes remains. The ease of the coronary sinus access in cardiac surgery as well as recent reports, and the present knowledge on the procedure as well as the availability of a new PICSO system, warrants this procedure to be evaluated clinically as a protection device in beating heart surgery, especially since catheter insertion into the coronary sinus is a clinical routine in many centres. Without the necessity of an active perfusion to achieve an improvement, the protocol in beating heart surgery does not have to be changed and makes this system an attractive supplement to the present routine.

We invite interested colleagues, performing more than 200 off-pump cases per year, to participate in a proposed multicenter trial (EASY Trial).

This clinical study will help to define the role of PICSO in beating heart surgery, as well as in interventional cardiology within the near future.

References