Visceral and Renal Tissue Oxygenation During Supraceliac Aortic Crossclamping and Left Heart Bypass with Selective Organ Perfusion

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Introduction. Left-heart bypass (LHB) and selective organ perfusion (SOP) are used during thoracoabdominal aortic surgery to prevent ischemic damage to the kidneys and visceral organs after supraceliac aortic crossclamping. We studied the hypothesis, in a porcine model, that despite LHB and maximal SOP, visceral and renal ischemia still occurred during surgery.

Material and methods. Eleven pigs (54–70 kg) were coupled to a non-pulsatile LHB with inflow and outflow at the lower thoracic and distal infrarenal aorta, respectively. After supracoeliac and infrarenal aortic crossclamping, SOP was started using perfusion catheters. The proximal and distal mean aortic blood pressures were kept above 70 and 50 mmHg, respectively, while the mean blood pressure within the SOP system was above 60 mmHg. The visceral and renal tissue oxygenation was measured by intermittent blood gas analysis, from the portal and both renal veins. The jejunal mucosal oxygenation was measured by tonometric measurement of the luminal pCO2.

Results. Measured median blood blood flow through the LHB and the SOP system were 800 and 1140 ml/min, respectively. Median blood flow prior to, and during LHB and SOP through the celiac artery, superior mesenteric artery, and left renal artery were 300 and 240, 762 and 295, and 235 and 235 ml/min, respectively. During 3 h of LHB and SOP no significant changes in the renal tissue oxygenation were noted compared with the physiological situation prior to supraceliac aortic crossclamping and cannulation. However, in the visceral vascular bed median mixed venous oxygen saturation dropped from 79 to 63% (p<0.001), and median oxygen extraction ratio increased from 26 to 41% (p<0.001). Median tonometric measured intraluminal jejunal pCO2 increased from 9.9 to 12.15 kPa (p<0.05). During 3 h of LHB and SOP no hemolysis was detected, as there was no rise in serum LDH.

Conclusion. LHB and SOP preserves renal but not visceral tissue oxygenation during supraceliac aortic crossclamping and does not induce hemolysis.

Key Words: Left heart bypass; Selective organ perfusion; Renal ischemia; Visceral ischemia; Hemolysis; Thoracoabdominal aortic aneurysm.
Selective Organ Perfusion

Material and Methods

Animal care and experimental procedures were performed in compliance with the National Guidelines for care of Laboratory Animals in the Netherlands. The study protocol was approved by the Animal Research Committee of the Academic Medical Center at the University of Amsterdam, the Netherlands.

Fifteen female Dutch farmbred pigs (54–70 kg) were studied. They were fasted except for ad libitum water for 16 h prior to induction of anesthesia. The animals were premedicated with intramuscular ketamine (15 mg/kg). Induction of anesthesia was performed with inhalation by mask of 2.0% isoflurane in a mixture of 50% O2 in air and 5 μg/kg sufentanyl intravenously. After induction of anesthesia, anesthesia was maintained with continuous infusion of ketamine 10 mg/kg/h and sufentanyl 5 μg/kg/h. Pancuronium bromide was used as needed for neuromuscular blockage. The pigs were endotracheally intubated and mechanically ventilated using Intermittent Positive Pressure Ventilation. The end-tidal CO2 concentration was kept between 4.8 and 5.3 kPa (36–40 mmHg) throughout the experiment. The proximal and distal arterial blood pressure was measured through intra arterial lines placed in the upper- and lower-limb arteries. The central venous pressure was measured in the superior caval vein. An intravenous catheter was placed in the left ear for fluid administration. During surgery continuous monitoring of ECG, oxygen saturation and body temperature was performed. The central venous pressure was kept around 10 mmHg throughout the experiment by infusion of saline and Ringers lactate to compensate for fluid losses. The arterial pO2 was always above 250 mmHg during the experiment and the arterial hemoglobin oxygen saturation was kept above 95%.

A median laparotomy was performed and the complete abdominal aorta and lower thoracic aorta was exposed after medial visceral rotation. The crus of the diaphragm was divided to facilitate exposure of the distal thoracic aorta. The inferior mesenteric artery, median sacral artery, and the lumbar arteries located between the celiac artery and renal arteries were ligated. The proximal celiac, superior mesenteric, and left renal artery were exposed and their blood flow measured with a flow meter (Transonic Systems, Ithaca, NY, USA). We did not measure the blood flow through the right renal artery because the approach to the aorta hinders isolation of the right renal artery. Both ureters were ligated distally and indwelling catheters were introduced in the proximal ureteric stumps, enabling selective kidney urine production registration. Intravenous catheters were placed for intermittent venous blood sampling in both renal veins and the portal vein. For determination of regional jejunal pCO2 a 16 Fr TRIP® tonometry catheter (Tonometrics, Datex-Engstrom Division, Helsinki, Finland) was introduced through the orogastric route and placed in the proximal jejenum. This catheter was connected to the TONOCA® monitor (Datex-Ohmeda, Finland) for semi-continuous automated air tonometry.

After administration of 100 mg heparin/kg the aorta was cannulated. The proximal arterial inflow cannula used was a Sarns® 6,5 mm High Flow right-angled cannula which was placed in the lower thoracic aorta about 3 cm proximal to the origin of the celiac artery. The distal cannula was a Sarns® 5 mm High Flow right-angled cannula and was placed in the aorta 3 cm distally to the lowest renal artery. The cannulas were connected to a Sarns® Delphin centrifugal pump, which was primed with saline, and so a LHB was created. The LHB consisted of 3/8th heparin coated tubing (Baxter, Uden, the Netherlands) and a Biotherm heat exchanger (A. B. Medical, Roermond, the Netherlands) which was connected to a heat exchanger pump (Hyp 10, Gambro, Sweden). After establishing a non-pulsatile aorto-aortic bypass with the LHB, the aorta was cross-clamped above the celiac artery and below the renal arteries. Between these clamps the aorta was opened longitudinally and the celiac, superior mesenteric artery, and both renal arteries were cannulated.
with 9 Fr Pruitt perfusion catheters connected to a four-catheter perfusion system (Duraflo coated DII Octopus set, Baxter, Uden, the Netherlands). This four-catheter perfusion system was placed as a side-arm on the LHB and so the SOP system was created. Transsonic flow meters were placed around the tube of the arterial inflow to the centrifugal pump, around all separate perfusion catheters, and around the tube leading to the the cannula in the distal abdominal aorta. Temperature was allowed to decrease to 34 °C, and was maintained at that level by means of the heat exchanger. The inflow to the centrifugal pump and outflow to the distal cannula and the four-catheter perfusion system was regulated according to the mean proximal and distal blood pressures. The proximal inflow of blood to the centrifugal pump was set as high as possible as long as the proximal mean blood pressure was above 50 mmHg. The outflow of the centrifugal pump was directed preferentially to the four-catheter system as long as the mean distal blood pressure was above 70 mmHg. So the SOP received the maximum blood flow within the limits set by the mean proximal and distal blood pressures. No red blood cell saver device (auto transfusion) was used during these experiments, because the blood loss during the procedures was less than 1000 ml.

The blood samples were analyzed with a conventional blood gas analyzer (ABL 505 device, Radiometer, Copenhagen, Denmark). All parameters (urine output, tonometry, and blood gas analysis of the blood samples) were recorded before installing the LHB and SOP system (T1), immediate after installing the LHB and SOP (T2) and at 30 min intervals for a total of 3 h (T3 – 8). In addition, blood samples were obtained at the same time intervals for analysis of hemolysis caused by the extracorporeal circulation. Serum lactate dehydrogenase (LDH) was used as hemolysis parameter.

**Statistical analysis**

Data are presented as medians. The data were categorized into two groups. The first are values prior to aortic cannulation, and the second are the values after aortic cross clamping and installing the LHB and SOP. The Wilcoxon signed-rank test was used to determine differences between these two related groups. P < 0.05 was considered statistically significant. The statistical analysis was performed with Statistical Package for the Social Sciences version 11.0.1 for Windows® (SPSS®, Chicago, Illinois, USA).

**Results**

During laparotomy two animals were found to have intra-abdominal disease (one cystic kidney with hydronephrosis and one hepatic parasite infection). Two animals died shortly after installing the LHB and SOP system because inadequate fixation of the aortic cannulas to the aorta lead to dislocation and massive lethal intra-operative hemorrhage. These animals were excluded from the study and analysis was performed on the remaining 11 animals.

Fig. 1 presents the mean blood pressures that were recorded during the experiments. The proximal mean blood pressure was kept above 70 mmHg, the mean distal pressure was kept above 50 mmHg, and the SOP system mean blood pressure was kept above 60 mmHg.

Fig. 2 represents the median blood flow through the LHB during the experiments. The blood flow through the LHB was stable around 800 mL/min. The median blood flow dropped significantly in the superior mesenteric artery from 762 to 295 mL/min (p < 0.01) and in the celiac artery from 300 to 240 mL/min (p = 0.03). The median blood flow in the left renal artery was unchanged at 235 mL/min. Both renal arteries showed a similar blood flow as shown in Fig. 2.

Fig. 3 shows the median mixed venous oxygen saturation in the portal vein, the right renal vein and left renal vein. There was no statistically significant change in the median oxygen saturation in both renal veins before and after LHB and SOP. This indicates preservation of regional renal tissue oxygenation during LHB en SOP. The median oxygen saturation in the portal vein before and during LHB and SOP was 79 and 63%, respectively (p < 0.01), indicating insufficient regional visceral tissue oxygenation during LHB and SOP.

The median values of the oxygen extraction ratio did not change significantly in both renal veins before and during LHB and SOP (Fig. 4). But in the portal vein the median oxygen extraction ratio increased from 26% before to 41% during LHB and SOP (p < 0.001).

The arterial-venous pH difference did not change significantly in both renal veins before and during LHB and SOP. But in the portal vein it increased from 0.08 to 0.13 (p < 0.001).

The tonometric measured intraluminal jejunal pCO2 increased non-significantly from 9.9 kPa before aortic crossclamping to 12.15 during LHB and SOP (p = 0.09).

Urine output from each kidney during LHB and SOP is presented in Fig. 5. Urine output was maintained during LHB and SOP. There was an
obvious difference in mean urine output at each time period between the left and right kidney, in favor of the right kidney. There was no rise in LDH during LHB and SOP. Therefore LHB and SOP do not cause hemolysis during this 3 h experiment.

Discussion

Although clinically significant visceral ischemia occurs in less than 5% of the patients operated for thoracoabdominal aortic aneurysms, it is still essential to prevent visceral ischemia because of its role in initiating and maintaining MOF. Several studies have indicated that visceral ischemia plays a key role in major post-operative complications such as SIRS and MOF. Hypoperfusion of the visceral circulation leads to loss of gut barrier function and permeability which permits translocation of bacterial pathogens into the systemic circulation. In addition, visceral ischemia leads to release of gut-derived chemical mediators which can cause distant organ damage. Minimal duration of visceral and renal ischemia
during thoracoabdominal aortic aneurysm repair can be achieved by using LHB and SOP\textsuperscript{9,13}.

In this study we investigated regional visceral and renal tissue oxygenation before and during LHB and SOP. We analyzed the blood gas parameters of the afferent organ venous blood as a direct way to assess the regional tissue oxygenation. Several studies have reported the usefulness of afferent blood gas parameters for monitoring the oxygenation of the studied organ and in principle, regional venous blood gas parameters can be measured from every organ of interest.\textsuperscript{14} We did not use lactate levels in the blood samples because lactate is a relatively late and uncertain marker of tissue oxygenation.\textsuperscript{15} We used the pig as the animal model to conduct our study. Pigs are commonly used in experimental vascular surgery because of the multiple similarities between the porcine and human anatomy and physiology. The diameters of the arteries in our model were identical to the human situation. The centrifugal pump, cannulas and perfusion catheters are also identical to those we use during thoracoabdominal aortic aneurysm surgery in humans. Because of these essential multiple similarities between our experimental model and the human, we feel our results can be extrapolated to the human situation.

We preferentially directed the blood flow, within the limits set by the mean proximal and distal blood pressure, to the SOP system. We choose a minimal proximal mean blood pressure of 70 mmHg to preserve adequate coronary and cerebral perfusion. The distal mean blood pressure was set at a minimal of 50 mmHg which is considered essential to prevent spinal cord ischemia. Despite our efforts to maintain maximal flow in the SOP system we could not prevent the occurrence of visceral hypoperfusion. As a result the visceral tissue oxygenation reduced significantly as was demonstrated by visceral mixed venous saturation, blood pH and oxygen extraction ratios.

Several experimental studies using visceral vascular occlusion have demonstrated that changes in blood flow to the gut wall are paralleled by concordant changes in tonometrically measured pCO\textsubscript{2} in the gastrointestinal lumen.\textsuperscript{16} In our study the tonometrically measured pCO\textsubscript{2} rose from 9.9 kPa in the physiologic pre-aortic crossclamp phase to 12.15 kPa after LHB and SOP. This increase was not statistically significant. Analysis of the gastrointestinal mucosal blood flow by tonometrically measuring the intraluminal pCO\textsubscript{2} are known to have many confounding factors.\textsuperscript{17,18} Whether this difference must be interpreted as a preservation of intestinal mucosal blood flow during SOP, or indeed as diminished mucosal blood flow is not clear from this study. It needs to be proven whether the reduced regional visceral tissue oxygenation found during LHB and SOP, in comparison with the physiological state, can prevent systemic release of gut-derived chemical mediators, compared with no visceral perfusion at all.

The median blood flow rates during LHB and SOP are more similar to each other than the median physiological blood flow rates. It can be hypothesized that the vascular resistance of this extracorporeal perfusion system (e.g. the lengths and diameters of the tubing, perfusion catheters, connection pieces) is the most important determinant of the measured bloodflow rates during the LHB and SOP. The peripheral vascular resistance of the visceral organs and kidneys is, during LHB and SOP, not the major determinant of the organ blood flow rate as it is in the physiological state. All the four perfusion catheters have the same vascular resistance in the SOP system which results in comparable blood flow rates to the visceral organs and kidneys. Perfusion of the superior mesenteric artery was performed with a standard 9 Fr perfusion catheter which just fitted in the ostium of the superior mesenteric artery. This was connected to the four-catheter perfusion system. Shorter catheters with larger diameters can be helpful in increasing the blood flow to the SOP system. A simple alternative would be to construct a large diameter direct side-branch from the extracorporeal system for selective perfusion of the superior mesenteric artery.

In our experiment, we used the non-pulsatile Sarns® Delphin centrifugal pump. Much research has been done about pulsatile and non-pulsatile total extracorporeal circulation.\textsuperscript{19–22} There are no reports on pulsatile LHB and SOP during repair of thoracoabdominal aortic aneurysms. Gear \textit{et al.} demonstrated that pulsatile total extracorporeal circulation causes less visceral ischemia than non-pulsatile total extracorporeal circulation.\textsuperscript{23} Further research about the effects of pulsatile LHB and SOP on the renal and visceral
tissue oxygenation during thoracoabdominal aortic surgery needs to be done. We demonstrated that LHB and SOP can preserve renal tissue oxygenation during supraclavical aortic crossclamping. Several studies demonstrated that renal tissue oxygenation is preserved in case of renal artery obstruction unless there is a stenosis with a more than 50% diameter reduction.\textsuperscript{24,25} Cold crystalloid renal artery perfusion is another method for renal protection during thoracoabdominal aortic aneurysm repair. It causes local renal hypothermia and so reducing the metabolic needs of the kidneys. Our results are in conflict with that of the group of Coselli who demonstrated, in a randomized clinical study, that cold crystalloid perfusion of the kidneys during thoracoabdominal aortic aneurysm repair leads to a better post-operative renal function preservation than blood perfusion.\textsuperscript{26} The SOP system they used was identical to ours but the total blood flow through the SOP system was only 400 ml/min in their study. Our median total SOP blood flow was 1005 ml/min. We demonstrated in our experimental study that the median physiological blood flow to the porcine renal artery was 235 ml/min, which can be maintained with the SOP system. In addition, we demonstrated that LHB and SOP result in continuous uninterrupted urine production during artificial perfusion. Intra-operative urine production is essential in preventing post-operative renal insufficiency. Jacobs \textit{et al.} demonstrated that perfusion pressure is an essential element in regulating intra-operative urine production.\textsuperscript{27}

We demonstrated a significant difference in urine production between the left and the right kidney. There was no significant difference in the blood flow through the right and left kidney during LHB and SOP. It can be hypothesized that the observed difference in urine production is a result of the opposite operative exposure. The left kidney is rotated to the right for adequate exposure of the aorta. This maneuver causes compression of the left kidney. In addition rotation can cause intermittent periods of arterial occlusion. This can have implications for patient selection and expected post-operative renal failure in patients with unilateral pre-existing renal disease.

Clinically significant hemolysis can be measured by elevation of the serum LDH. During our experiments, no rise of the serum LDH occurred. In our study we choose a maximal period of 3 h for the LHB and SOP, because the majority of extracorporeal circulation times during repair of thoracoabdominal aortic aneurysms are less than 2 h. Curtis \textit{et al.} reported no signs of hemolysis when using different centrifugal pumps for less than 4 h in \textit{in vitro} and \textit{in vivo} studies.\textsuperscript{28,29} In their study, the Sarns\textsuperscript{1} pump, which we used in this study, does not lead to elevation of the LDH within 5 h pumping. Many authors agree that centrifugal pumps are ideally suited for LHB during surgery on the thoracic aorta because they are relative simple to operate and do, contrary to roller pumps, not require full heparinization.\textsuperscript{3,29,30} We demonstrated that incorporating the SOP system on the centrifugal LHB system does not lead to significant hemolysis during 3 h of bypass.

In conclusion, LHB and SOP can maintain intra-operative renal perfusion and function without inducing intra-operative hemolysis. However, it cannot maintain visceral perfusion and tissue oxygenation.

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\textbf{References}


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