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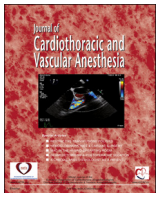

Original Article

Muscle Tissue Saturation Compared With Muscle Tissue Perfusion During Low Blood Flows: An Experimental Study

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Objective: To investigate whether changes in muscle tissue perfusion measured with positron emission tomography would be reflected by parallel changes in muscle tissue oxygen saturation (StO_2) measured using near-infrared spectroscopy during high and low blood flow levels achieved using cardiopulmonary bypass (CPB) in an animal model.
Design: A prospective, randomized study.
Setting: Research laboratory, single institution.
Participants: Eight pigs (69-71 kg).
Interventions: In anesthetized pigs, normothermic CPB was established with a blood flow of 60 mL/kg/min for 1 hour. Thereafter, a low blood flow of either 47.5 or 35 mL/kg/min was applied for 1 hour followed by a blood flow of 60 mL/kg/min for an additional hour. Regional StO_2 was measured continuously by placing a near-infrared spectroscopy electrode on the skin above the gracilis muscle of the noncannulated back leg. Muscle tissue perfusion was measured using positron emission tomography with ^{15}O-labeled water during spontaneous circulation and the different CPB blood flows. Systemic oxygen consumption was estimated by measurement of venous saturation and lactate levels.
Measurements and Main Results: The results showed profound systemic ischemia during low CPB blood flow. StO_2 remained high until muscle tissue perfusion decreased to about 50%, after which StO_2 paralleled the linear decrease in muscle tissue perfusion.
Conclusion: In an experimental CPB animal model, StO_2 was stable until muscle tissue perfusion was reduced by about 50%, and at lower blood flow levels, there was almost a linear relationship between StO_2 and muscle tissue perfusion.

Key Words: animal study; cardiopulmonary bypass; near-infrared spectroscopy; muscle tissue perfusion; regional blood flow; positron emission tomography

IDENTIFICATION OF LOW blood flow during cardiogenic, hemorrhagic, or septic shock involves measurement of global oxygenation, hemodynamic variables, and blood lactate levels.[1] More information about the regional microcirculation can be acquired using technologies including microdialysis,

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gastric tonometry, tissue oxygen tension electrodes, sublingual capnometry, and near-infrared spectroscopy (NIRS).[2] NIRS is the most widely used method due to its applicability.[3] In patients undergoing cardiac surgery, reduced striated muscle tissue oxygen saturation (StO_2) measured using NIRS at the thenar eminence is an earlier indicator of inadequate blood flow than blood lactate.[4] Moreover, hypovolemia has been demonstrated to be associated with significantly decreased StO_2 in volunteers.[5] Consistent with these findings, the authors previously demonstrated that StO_2 was an accurate marker of insufficient muscle tissue perfusion despite restored systemic blood flow in a pig model.[6] In contrast, a blood loss of 500 mL in blood donors did not reduce StO_2[7] and normal StO_2 values may be seen in patients experiencing hypovolemic shock.[8]

Blood flow to the muscles and muscle tissue perfusion are governed by central and humoral factors that can lead to vasoconstriction and centralization of muscle blood flow to vital organs during low-flow conditions.[9] Characteristically, muscle tissue in the resting state has a low metabolic rate, and consequently a decrease in StO_2 should first appear, theoretically, when muscle perfusion is markedly reduced. This is consistent with results from a previous experimental study[6] demonstrating that during cardiopulmonary bypass (CPB) only minor changes in StO_2 occurred at moderately reduced CPB flow and significant reductions in StO_2 appeared when the CPB flow was reduced by 50%. Thus, regional muscle StO_2 may be used to detect only severe reductions in blood flow. If so, this could explain the contradictory results from the aforementioned studies and brings into question the presumed ability of StO_2 to act as an early risk indicator of insufficient blood flow and tissue perfusion in the clinical setting. However, there are no studies, to the authors' knowledge, that have examined the relationship between the regional blood flow and StO_2. An accurate method of measuring regional muscle flow is positron emission tomography-computed tomography (PET-CT).[10] The aim of this study was to investigate, with controlled high and low blood flow levels using CPB, whether changes in muscle blood flow measured with PET would be reflected in changes in StO_2 measured using NIRS.

Methods

Eight female Danish Landrace x Yorkshire pigs (69-71 kg) were used. The Danish Animal Experiments Inspectorate approved the study (No. 2013-15-2934-00992), which was performed in accordance with the European Convention for the Protection of Animals used for Experimental Purposes (Council of Europe, 2010/63/EU). Pigs were purchased from a commercial pig supplier. After at least 5 days of acclimatization, the pigs were fasted overnight with free access to tap water. To ensure that only healthy animals were used in the experiment, the pigs were examined clinically by a veterinarian before anesthesia was initiated.

Instrumentation and Monitoring

The pigs were premedicated with an intramuscular injection of midazolam, 70-to-75 mg, and ketamine, 350-to-375 mg. Anesthesia was induced with an intravenous (IV) bolus injection of propofol, 50-to-100 mg, through an ear vein catheter and was maintained with continuous IV infusions of propofol, 200-to-600 mg/h, and fentanyl, 1,000-to-2,000 μg/h. Muscle relaxation with IV pancuronium (350 mg/h) was started after adequate anesthesia had been confirmed by the absence of reaction to painful stimulation in the animals' front hooves. The trachea was intubated (Portex, 7.5-mm; Smiths Medical, Ashford, UK), and the lungs were mechanically ventilated (Datex-Ohmeda S5 Advance; GE Healthcare, Little Chafont, UK) with a tidal volume of 6-to-8 mL/kg, inspiratory: expiratory ratio of 1:2, positive end-expiratory pressure of 5 cmH_2O, and fraction of inspired oxygen of 0.6. The respiratory rate (14-16 breaths/min) was adjusted to achieve normal partial pressure of arterial carbon dioxide with an arterial pH of 7.4. During CPB, the respiratory rate was reduced to 4 breaths/min.

An arterial line (7-Fr, Radifocus Introducer II; Terumo Interventional Systems, Leuven, Belgium) was inserted into a right carotid artery branch for continuous measurement of blood pressure and intermittent blood gas analyses. A venous line (7-Fr, Radifocus Introducer II) was introduced transcutaneously into the jugular vein for measurement of central venous oxygenation saturation ($ScvO_2$). Core temperature was measured with a rectal probe. Cardiac rhythm was monitored with 3-lead electrocardiography. A urinary bladder catheter was inserted via the urethra for measurement of diuresis.

CPB was established between a 29-Fr, 3-lumen venous catheter (Medtronic Inc, Minneapolis, MN) in the upper caval vein placed via the right jugular vein and a 19-Fr arterial catheter in the lower aorta placed via the right femoral artery (Medtronic Inc). The CPB circuit consisted of a centrifugal pump (Rotaflow; Maquet, Rastatt, Germany) and an oxygenator with a heat exchanger (Jostra Quadrox D Diffusion Membrane; Maquet). The system was heparin-coated (Bioline Coating; Maquet) and primed with isotonic saline. On initiation of CPB, cardiac arrest was achieved by inducing ventricular fibrillation via an intravenous pacemaker wire and a 9-volt battery. The CPB flow was set to 60 mL/kg/min to obtain normal systemic circulation; anesthetized adult pigs have a cardiac output of 5-to-6 L/min (62.5-75 mL/kg/min), which is only slightly different from the initial blood flow of humans.[6,11] After initiating blood flow of 60 mL/kg/min, a 30-minute steady-state period was allowed. The blood flow of 60 mL/kg/min was continued for another 60 minutes before the PET-CT scan was performed. Thereafter, the animals were allocated randomly to 1 of the following 2 groups: a CPB blood flow of 47.5 mL/kg/min (group I) or 35 mL/kg/min (group II), followed by a 30-minute steady-state period. After another 60 minutes at these flow rates, PET-CT was performed. Blood flow then was restored to 60 mL/kg/min, and a 30-minute steady state was allowed; thereafter, an additional 60 minutes of flow at 60 mL/kg/min was initiated before the last PET-CT was performed (Fig 1). Throughout the study, normothermic CPB was obtained (ie, 38°C-39°C), equivalent to the normal core temperature of an adult pig, and heparin was administered to achieve an activated clotting

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