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MAIN TEXT

Ocular surface microcirculation is better preserved with pulsatile versus continuous flow during cardiopulmonary bypass—An experimental pilot

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Abstract

Background: Non-pulsatile cardiopulmonary bypass (CPB) may induce microvascular dysregulation. In piglets, we compared ocular surface microcirculation during pulsatile versus continuous flow (CF) bypass.

Methods: Ocular surface microcirculation in small tissue volumes (~0.1 mm^3) at limbus (high metabolic rate) and bulbar conjunctiva (low metabolic rate) was examined in a porcine model using computer assisted video microscopy and diffuse reflectance spectroscopy, before and after 3 and 6 h of pulsatile ($n = 5$ piglets) or CF ($n = 3$ piglets) CPB. Functional capillary density, capillary flow velocity and microvascular oxygen saturation were quantified.

Results: At limbus, velocities improved with pulsatility ($p < 0.01$) and deteriorated with CF ($p < 0.01$). In bulbar conjunctiva, velocities were severely reduced with CF ($p < 0.01$), accompanied by an increase in capillary density ($p < 0.01$). Microvascular oxygen saturation decreased in both groups.

Conclusion: Ocular surface capillary densities and flow patterns are better preserved with pulsatile versus CF during 6 h of CPB in sleeping piglets.

KEYWORDS

bulbar conjunctiva, capillaries, capillary flow velocity, functional capillary density, limbus, mechanical circulatory support, microcirculation, microvascular oxygen saturation, ocular surface, ODIN concept, pulsatile versus continuous flow

1 | INTRODUCTION

Continuous flow (CF) pumps for cardiopulmonary bypass (CPB) are reliable and cost effective, and mortality rates related to standard open-heart surgical procedures are low. However, in patients supported with CF pumps for days, that is, during extra corporeal membrane oxygenation (ECMO), morbidity and mortality rates remain high both during and for months following treatment.[1–3] Biological evolution has favored pulsatile flow (PF) in circulatory systems among vertebrates,[4] but CF pumps are still preferred for CPB and ECMO despite evidence that PF better preserves microcirculation in end organs.[5,6]

Circulatory failure occurs when the respiratory and cardiovascular systems supply insufficient amounts of oxygen to meet the metabolic demands of all the cells of the body. Clinical medicine lacks technologies for direct assessments of oxygen delivery from the microcirculation to cells. Macro- and microvascular parameters are known to be dissociated during circulatory failure,[7] and there is a compelling need for new methods to monitor microcirculatory function.[8]

The non-invasive oxygen delivery index (ODIN) concept for assessments of microvascular function, includes technologies (computer assisted video microscopy—CAVM and diffuse reflectance spectroscopy—DRS), data acquisition protocols and analyses that can be used for estimating the capacity for oxygen delivery from the microcirculation to cells in volumes of ~0.1 mm^3[9–15] by quantifying functional capillary density (FCD), capillary flow velocities (CFV) and microvascular oxygen saturation ($SmvO_2$).

A correlation between cerebral and ocular surface microcirculation (i.e., conjunctiva) has previously been demonstrated both in animals and in humans.[16,17] Arterial ophthalmic supply derives from both the internal carotid artery via the ophthalmic artery, and from the external carotid artery via the temporal and maxillary arteries.[18] Ocular surface microcirculation may therefore represent a surrogate measure of brain perfusion in patients with systemic circulatory failure. The *limbus,* a metabolically active circumferential transition zone (~0.6 mm) between the avascular cornea and bulbar conjunctiva has a high concentration of stem cells continuously regenerating the corneal epithelium. The *bulbar conjunctiva* is assumed to have more scattered stem cells, a lower metabolic rate and vessels transport oxygenated blood to reach limbal capillaries. In sleeping piglets, we have shown that the ODIN concept can be used to estimate oxygen delivery to conjunctival cells, and also that the microvascular capacity to deliver oxygen was greater at limbus than the bulbar conjunctiva, compatible with a higher metabolic rate at limbus.[12]

In the present study, our hypothesis was that ocular surface microcirculatory function is better preserved with PF as compared with a CF pump. During 6-h CPB, we used the ODIN concept to compare effects on limbal and bulbar conjunctival microcirculation in sleeping piglets assigned to either PF or CF.

2 | MATERIAL AND METHODS

The ODIN concept was used for ocular surface measurements at baseline (before skin incision), 3 h and 6 h in eight healthy female Yorkshire piglets (44 ± 4 kg) supported with PF (VentriFlo True Pulse Pump®, Design Mentor Inc, Pelham, NH, USA) ($n = 5$) or CF (Rotaflow®, Maquet Holding BV & Co. KG, Rastatt, Germany) ($n = 3$) pumps.

During data collection, each recorded file was labeled with a code. The analyzer was blinded to type of heart pump and time of recording. The study protocol (2016-1659) was approved by Institutional Animal Care and Use Committee at Cleveland Clinic. The piglets were treated in compliance with the Guide for Care and Use of Laboratory Animals and institutional guidelines.

2.1 | Preoperative piglet preparation

The piglets were quarantined and monitored at the laboratory facility for at least three days and fasted 12 h before surgery. Premedication—xylazine (2 mg/kg, IM) and ketamine (20 mg/kg, IM)—was administered and vital signs (respiratory rate, appetite, general condition) monitored. Anesthesia was induced by propofol (1 mg/kg, IV) or buprenorphine (0.05 mg/kg, IV), and was maintained throughout the experiment by volatile isoflurane (1.0–3.0%). Fraction of inspired oxygen was set to 80% before CPB and lowered to 50% during CPB. To prepare the neck, groin, and chest for open chest surgery, the piglets were fixated in a supine position with attached ECG leads to the extremities. Lidocaine (<2 mg/kg/h IV) was injected to prevent ventricular arrhythmia. Arterial monitoring lines were inserted in the carotid artery and a venous pressure line in the jugular vein.

2.2 | CPB procedure and sampling of blood gas

The pericardium was opened following a median sternotomy. A pulmonary artery flow probe was used to measure cardiac output and to control that flow was kept at 0 L/min during CPB. Cannulas were inserted through the right

atrial appendage into the ascending aorta and the inferior vena cava (22 Fr EOPA® [elongated one-piece] Arterial Cannula, Medtronic Perfusion Systems, Minneapolis, MN, or 21 Fr Arterial Cannula, Edwards Lifesciences, Irvine, CA and 34–46 Fr or 29–37 Fr MC2 Two-Stage Cannula, Medtronic Perfusion Systems, Brooklyn Park, MN). A vent tube, inserted in the left atrium or ventricle, prevented ejection of blood.

After heparin (500 U/kg, IV) was administered and when activated clotting time exceeded 450 s, CPB was engaged at a flow rate of 50 ml/kg/min throughout the procedure. One of the following oxygenators were used in the circuit; Quadrox (Maquet Holding BV & Co. KG, Rastatt, Germany), Affinity Fusion (Medtronic, Minnesota, USA) or Capiox (Terumo Cardiovascular Systems, Tokyo, Japan). Vasoactive agents were not administered during CPB. Arterial blood gas samples were drawn hourly. After 6 h on CPB under deep anesthesia (isoflurane 5%), an additional dose of heparin (500 U/kg, IV) was administered. The piglets were sacrificed by a lethal dose of potassium chloride (2.5–3.5 mEq/kg, IV).

2.3 | Microcirculatory measuring techniques, parameters and recording procedures

The eyelids of the left eye were retracted by sutures during measurements and closed between recordings. Saline was applied to maintain a moist ocular surface between measurements.

Microvascular data from the limbal and bulbar conjunctiva was captured with the ODIN concept.[12] In brief, films of 20 s duration were recorded by CAVM with a 300 × magnification lens attached to a digital microscope (Optilia, D1, Instruments AB, Sollentuna, Sweden) with autofocus, 1.13 mm × 0.7 mm field of view, frame rate 7 frames/s and image resolution 1920 × 1080 pixels. At least four film sequences from each conjunctival region were recorded at baseline, and at 3 h and 6 h thereafter.

Capillaries, identified as visible blood vessels <20 μm, which crossed six parallel grid lines separated by 100 μm, were counted. FCD was expressed as capillary crossings/mm line. CFV was determined at each crossing according to a previously defined 6-category velocity scale ranging from category 0 (no flow) to category 5 (brisk flow).[12]

To measure $SmvO_2$ in tissue volumes of ~0.1 mm^3, we used DRS; a spectrometer (AvaSpec-2048-2, Apeldoorn, The Netherlands) with a tungsten halogen light source (AvaLight-HAL, Apeldoorn, The Netherlands) and spectral range of 450–800 nm. The fiber optic probe was calibrated against a white polytetrafluorethylene tile (WS-2, Avantes, The Netherlands) before each set of recordings. The positioning of the DRS probe was not sufficiently precise to discriminate between limbal and bulbar recordings.

The equipment was moved slightly between each recording to capture different measuring volumes.

2.4 | Data analysis and statistics

Custom-made software (EyeSoft version 1.0, ODI Medical, Oslo, Norway) was used to analyze CAVM films and to calculate DRS-determined $SmvO_2$.[12]

Statistical analyses were conducted in SPSS version 26 (SPSS Inc, Chicago, Illinois, USA). Continuous variables are expressed as mean ± SD. An independent samples *t*-test was used to compare CF and PF pumps for the FCD and $SmvO_2$ parameters. Graphical displays of these data are box-whisker plots presenting median, 25th and 75th percentiles, range and outliers. A chi square test was used to compare categories for CFV. A p-value < 0.05 was considered statistically significant.

3 | RESULTS

During this experiment, mean arterial pressure for the pumps varied between 33–38 mm Hg (PF) and 30–39 mm Hg (CF) with a pulse pressure between 23–34 mm Hg (PF) and 4–5 mm Hg (CF). A detailed presentation of hemodynamics is given elsewhere.[19] Microscopy films and DRS spectra were collected without adverse events. Numbers, location and time of analyzed capillaries and spectra are given in Table 1.

3.1 | Capillary flow velocity

The majority of CFV-scored capillaries were in category 0 (no flow) and 3 (CF). Category 4 (rapid flow) was rarely observed (<4% of measurements) and category 5 (brisk flow) was never observed.

In limbal recordings, the PF piglets decreased category 0 and increased category 3 CFV-scores during the 6 h experiment, $p < 0.01$ (Figure 1A,C). The opposite CFV pattern was seen in CF piglets, $p = 0.01$ and $p < 0.01$ (Figure 1B,D). In bulbar conjunctiva, category 3 decreased and category 0 increased for both pumps ($p < 0.01$), but only CF piglets had critically low CFV after 6 h (Figure 1E–H).

3.2 | FCD

At baseline, ocular surface FCD of all piglets was higher at limbus (11.3 ± 3.0) as compared with bulbar conjunctiva

TABLE 1 Total numbers of examined capillaries/spectra for assessment of each parameter

Anatomical location	Total number of examined capillaries	Baseline		3 h		6 h	
		PF	CF	PF	CF	PF	CF
Limbus	FCD	224	302	217	318	252	279
	CFV	103	182	166	212	176	229
Bulbar conjunctiva	FCD	101	107	107	135	531	52
	CFV	75	101	96	130	370	49
Conjunctiva	$SmvO_2$	55	35	58	36	60	36

Abbreviations: CF, continuous flow; CFV, capillary flow velocity; FCD, functional capillary density; PF, pulsatile flow; $SmvO_2$, microvascular oxygen saturation.

(7.1 ± 2.8), $p < 0.01$. Piglets supported by PF had a stable FCD throughout the study both at limbus and in bulbar conjunctiva, whereas piglets aided by CF increased bulbar conjunctival FCD after 6 h, $p < 0.05$ (Figure 2B).

3.3 | DRS

Average arterial oxygen saturation for all measurements in piglets throughout the experiment was 99% and no measurement was below 96%. Ocular surface $SmvO_2$ decreased over time independent of pump (Figure 3). No significant differences were seen between the two pumps at baseline, 3 and 6 h.

4 | DISCUSSION

In the current study we utilize the ODIN concept to assess ocular surface microcirculation in sleeping piglets assigned to PF or CF pumps during 6 h of CPB. Piglets supported on PF had a higher percentage of capillary category 3 flow (optimal velocity) both at limbus and in bulbar conjunctiva as compared with CF (Figure 1C vs. 1D, and Figure 1G vs. Figure 1H) after 3 h. These differences were even more pronounced after 6 h. Ocular surface FCD was unaffected in PF piglets, while CF triggered increased FCD compatible with capillary recruitment, after 6 h (Figure 2B), possibly caused by hypoxia.

Oxygen delivery from capillaries is vital for all cells, and is dependent on an interaction between several factors, including our set of parameters. Low CFV facilitates oxygen extraction (i.e., equilibration of oxygen between the erythrocytes and the surrounding tissue), due to long capillary erythrocyte transit time, but since few erythrocytes pass through the capillary network, oxygen delivery is low. Higher CFV shortens transit- and equilibration time for oxygen extraction from each erythrocyte—the capillary serves as a physiological arteriovenous shunt—but oxygen delivery is maintained due to the large number of erythrocytes passing through the capillary.

In healthy humans using the present velocity scale, category 3 CFV is seen in >80% of skin nutritive papillary capillaries.[13] Low velocities at baseline in this study may be related to the examined tissue (ocular surface) or the experimental model (supine position of piglets and administered anesthetic drugs). At limbus, category 3 CFV increased and category 0 decreased in the PF piglets over time (Figure 1A,C), meaning that CFV optimized throughout the 6 h on CPB. The opposite CFV patterns were observed for the CF piglets (Figure 1B,D), indicating that oxygen delivery was compromised. In bulbar conjunctiva, percentages of capillaries in category 3 after 6 h were acceptable for PF, and critically low for CF (Figure 1G,H).

In the present study, limbal FCD at baseline was higher in the CF piglets as compared with the PF piglets (Figure 2A), but no changes between the two groups were seen at limbus for the next 6 h on pump. In bulbar conjunctiva the two groups had similar FCD, except for an increase in CF piglets after 6 h (Figure 2B). This recruitment of capillaries was coexisting with the mentioned critically low CFV in CF piglets (Figure 1F,H) and is interpreted as a compensatory mechanism to maintain oxygen delivery.

Decreased $SmvO_2$ observed in both groups after 3 and 6 h indicates increased tissue oxygen extraction (arterial oxygen saturation—$SmvO_2$). Arterial oxygen saturation was >96% throughout the experiment, but both pumps in this model failed to maintain unaltered $SmvO_2$. The limbus is <1 mm wide, and we did not have sufficient precision of probe placement to discriminate between limbal and bulbar recordings. We believe that the greater part of recorded $SmvO_2$ values (Figure 3) represent bulbar conjunctiva and that the results are inconclusive with regards to oxygen extraction at limbus (high metabolic demand).

Worldwide state-of-the-art CPB and ECMO are conducted with CF pump despite publications indicating that PF is superior to CF.[6,17,20–24]

Various study designs, methods and endpoints have been used to study microvascular function related to CF or PF pumps. Studies using side-stream dark field imaging or orthogonal polarization spectral imaging state that sublingual FCD, perfused vessel density and proportion

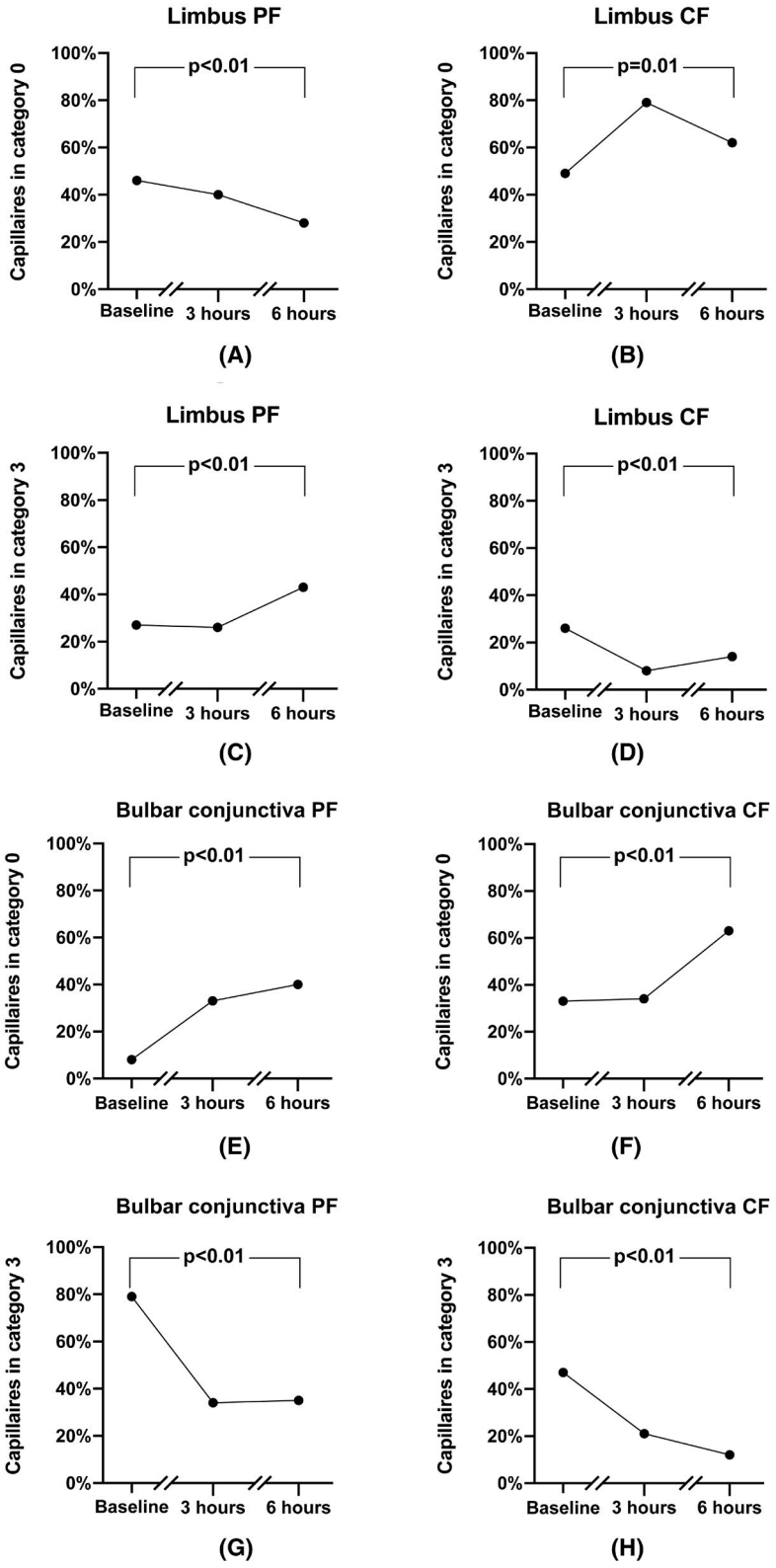

FIGURE 1 Capillary flow velocity at limbus (A–D) and bulbar conjunctiva (E–H). Dots represent percentage of all recordings for each pump at baseline, three and six hours. CF, continues flow; PF, pulsatile flow

of perfused vessels worsen during CPB, but are inconclusive regarding the significance of pulsatility.[25] Zhao et al recently showed that bulbar conjunctival microcirculation, examined in our study, better reflects perfusion in the central nervous system as compared with sublingual mucosa.[17]

Frequency of complications related to CPB rise when surgery exceeds 180 min.[26] In the present study, changes in microvascular function in favor of PF developed between 3 and 6 h, while studies failing to demonstrate benefits of PF, often are limited to less than 3 h on pump.[27] Our findings correspond with the clinical

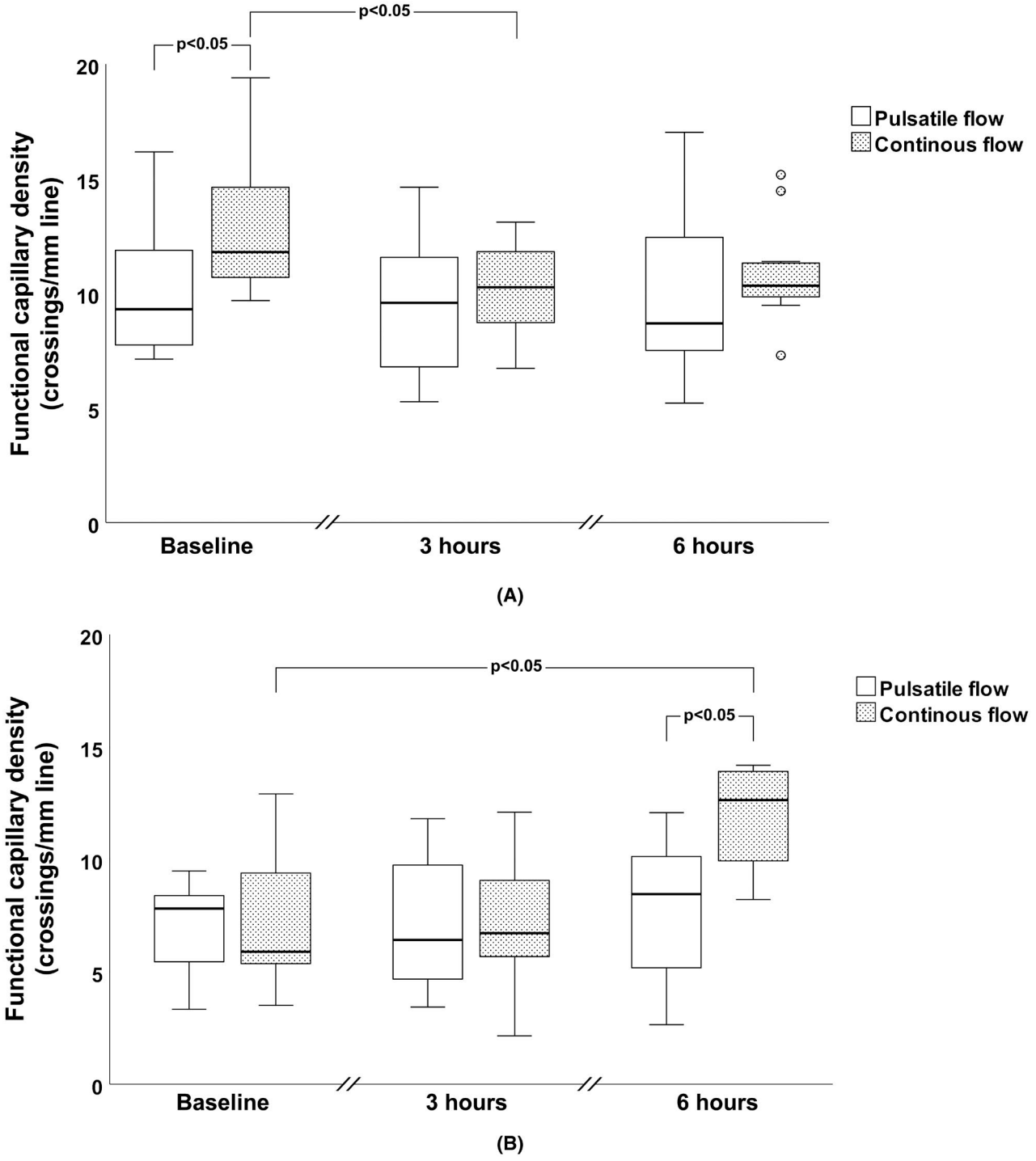

FIGURE 2 Functional capillary density at limbus (A) and bulbar conjunctiva (B) in piglets supported by pulsatile and continuous flow

experience that short term procedures (e.g., uncomplicated CPB) have good outcomes, while long term CF ECMO treatment is associated with high morbidity and mortality rates.[1–3]

There are some important limitations to this study. Administered drugs and supine posture may have affected the results. In addition, sample sizes differed between the two groups (five PF piglets vs. three CF piglets). A number of films also had inferior quality and could not be analyzed. This study is only the second report of ocular surface ODIN measurements, and both handling of the equipment and the analyzing platform could be refined.

In conclusion, results in this study indicate that ocular surface capillary densities and flow patterns are better preserved in piglets supported by PF, as compared with CF during 6 h of CPB.

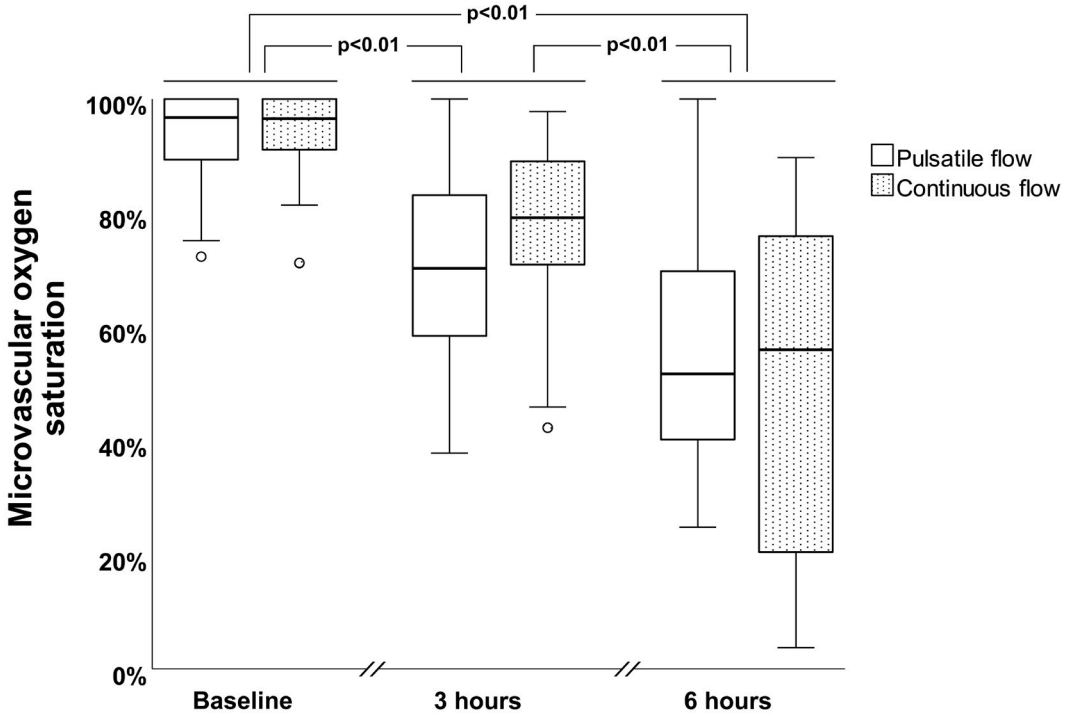

FIGURE 3 Microvascular oxygen saturation piglets at baseline, three and six hours

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CONFLICT OF INTEREST

The ODIN concept is patented in Japan, and a patent is pending in USA and Europe. Knut Kvernebo is founder, shareholder and currently CMO of ODI Medical AS. Måsøy SE is shareholder in ODI Medical. Knut Kvernebo and Anne Kari Kvernebo are related. ODI Medical AS has provided the analysis platform used in this study. Remaining authors have no financial conflicts of interest.

AUTHORS CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection were performed by Takuma Miyamoto, Raymond Dessoffy, Kiyotaka Fukamachi, Anne Kari Kvernebo, Knut Kvernebo. File analyses were performed by Anne Kari Kvernebo, Knut Kvernebo and Svein-Erik Måsøy. All authors participated in data interpretation. The draft of the manuscript was written by Anne Kari Kvernebo. All authors commented, read and approved the final manuscript.

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