Blood flow measurements within optic nerve head during on-pump cardiovascular operations. A window to the brain?

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Abstract

This observational study is conducted to demonstrate optic nerve head (ONH) blood flow alterations during extracorporeal circulation (ECC) in routine on-pump cardiovascular operations in order to evaluate the perfusion status of important autoregulatory tissue vascular beds during moderate hypothermia. Twenty-one patients free from eye disease were prospectively enrolled in our database. Perioperative ONH blood flow measurements were performed using a hand-held portable ocular laser Doppler flowmeter just after administration of general anesthesia and during cardiopulmonary bypass (CPB) upon the lowest temperature point of moderate hypothermia. Important operative flow variables were correlated to optic nerve blood flow during surgical phases. Statistical analysis showed significant reduction of $32.1 \pm 14.5\%$ of mean ONH blood flow in phase 2 ($P<0.0001$) compared to the reference flow values of phase 1. A negative univariate association between ECC time and ONH blood flow in phase 2 ($P=0.031$) is noted. This angiokinetic approach can detect changes of flow within autoregulatory vascular tissue beds like ONH, thus creating a ‘window’ on cerebral microvasculature. ONH blood flow is reduced during CPB. Our data suggest that it is of paramount importance to avoid extracorporeal prolongation even in moderate hypothermic cardiovascular operations.

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Keywords: Extracorporeal circulation; Cardiopulmonary bypass; Laser Doppler flowmeter; Optic nerve head blood flow measurements

1. Introduction

The use of extracorporeal circulation (ECC) is fundamental for the majority of cardiac operations. Despite continuous technical improvements, multiple organ dysfunctions after ECC are still a significant clinical problem. Apparently, the optic nerve head (ONH) does not avoid the consequences of perfusion changes during ECC, even though it is largely protected by its own autoregulation system under physiological conditions [1]. The present angiokinetic study tries to evaluate possible hypoperfusion phenomena provoked by ECC through a non-invasive technique, using a portable ocular laser Doppler flowmeter (LDF) to estimate blood flow changes in ONH during routine cardiovascular operations.

2. Patients and methods

2.1. Patients

Twenty-one patients with no significant eye disease that underwent cardiac surgery were prospectively enrolled in our database. Their fundus was approached by measuring the blood velocity and blood flow within the vessels of the ONH through a portable-ocular laser Doppler red blood cell flowmeter [2] during ECC in bypass grafting and valve replacement surgery. Only the pupil of the measured eye received three drops of midriatics (tropicamide) twice within an interval of 10 min.

Patients with a previous history of fundus disease (retinopathy) or glaucoma or eye surgery, history of stroke, neurological or psychiatric illness, renal insufficiency, systemic disease, thromboembolic events, carotid artery disease, allergy to anti-coagulant or anti-thrombotic drugs and carotid stenosis $>50\%$ as demonstrated by carotid duplex sonography were excluded.

The study adhered to the tenets of University of Larisa, was approved by the Healthcare Trust Ethics Committee and all patients gave informed consent.
2.2. Measurements by LDF

A hand-held ocular laser Doppler system for measurement of red blood cell velocity and blood flow in the ONH was used (Fig. 1). The instrument is based on the well-established LDF techniques and principles. The optical systems for the delivery of the probing laser beam at the ONH tissue and detection of the light scattered by the red blood cells (RBCs) moving in this tissue have been implemented in a portable Kowa Genesis fundus camera that provides illumination and viewing of the fundus [2].

Although not providing absolute data, the LDF technique allows linear measurements of flow changes induced by physiological, pharmacological and pathological conditions [2, 3]. The device and software analysis program were developed by the University of Applied Sciences of Western Switzerland (Sion, Switzerland). The operator of the flowmeter received proper training regarding the use of the flowmeter under the conditions pertaining to this study.

2.3. Study protocol

Our perioperative protocol included several ONH blood flow measurements at different disk sites during two phases of the surgical cycle (Fig. 2). Initially, we performed multiple flow measurements at the same site 30 min after general anesthesia in each patient, using them as reference points of our baseline data (phase 1). Then measurements were performed again during ECC, at the lowest temperature point of moderate hypothermia (phase 2).

Particularly several operative variables which are important flow determinants [carbon dioxide arterial pressure (PCO$_2$), intraocular pressure (IOP), hemoglobin (Hg), mean arterial pressure (MAP), temperature (T), ECC time and aortic clamping time in phase 2] were elected to be analyzed with the LDF results [1].

2.4. Statistical analysis

The agreement of direct current (DC) values between phases 1 and 2 was assessed by Lin’s correlation coefficient of concordance. Summary statistics of all studied variables are demonstrated as in mean ± S.D. Univariate analysis included Pearson’s correlation coefficient in order to assess the linear association between flow variables and ONH blood flow. The mixed effect model for repeated measurements was used to investigate the influence of percentage differences of flow variables to ONH blood flow alterations using patients as a random factor. The best covariance structure was tested with Akaike Information Criterion (AIC). All tests were two-sided and the level of statistical significance was set at 0.05.

3. Results

The patients consisted of 18 males and three females aged from 39 to 78 years with a mean age of 65.7 years. Eighteen of them underwent coronary aortic bypass grafting (CABG), one underwent atrial septal defect repair and in two patients a combination of CABG and aortic valve replacement was performed.

Substantial DC concordance correlation coefficient was achieved. The percentage DC distance between phases is registered as 1.98 ± 3.09%, concordance coefficient (pc) = 0.9839 (Table 1). From the means calculations, a decrease of ONH blood flow of 32.1 ± 14.5% between the two phases was registered (Fig. 3). A multivariate correlation analysis of changes of clinical parameters with fluctuations of ONH blood flow from phase 1 to phase 2 is depicted in Table 2. These parameters included the proportional percentage difference of MAP, IOP, PCO$_2$, T and Hg concentration. Phase 1 constitutes the reference point for comparison and appreciation of operative variables. The analysis result derived
Table 1. Validation outcome of laser Doppler results. The DC is proportional to the intensity of the light incident on the detector. For repeated measurements from the same site of the disk, it is very important to maintain this parameter constant to ensure that the variations of the flow parameters are not due to variations in the intensity of the probing beam at the fundus or variations in the site of measurements. DC values between phases are <10% of its mean value

<table>
<thead>
<tr>
<th>Variable</th>
<th>Label</th>
<th>n</th>
<th>Mean</th>
<th>S.D.</th>
<th>(pc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC12</td>
<td>DC ph 1–2 % distance</td>
<td>21</td>
<td>1.98</td>
<td>3.09</td>
<td>0.9839</td>
</tr>
</tbody>
</table>

DC, direct current; n, number of patients; strength of agreement, Lin’s concordance correlation coefficient (pc.). Almost perfect: >0.99; substantial: 0.95–0.99; moderate: 0.90–0.95; poor: <0.90.

Fig. 3. Demonstration of optic nerve head blood flow in phase 1 and 2.

from the mixed procedure is that ONH blood flow is significantly reduced in phase 2 compared to the reference flow values of phase 1 ($P^{-1}<0.0001$). The multivariate associations between the above clinical parameters and flow changes showed no significance. Additionally, there is a negative univariate association between ECC time and ONH blood flow during phase 2 ($r=-0.50$, $P=0.031$) (Fig. 4).

Table 2. Multivariate analysis of important operative flow variables correlated to flow changes of optic nerve head microcirculation. The mixed procedure between phases

<table>
<thead>
<tr>
<th>n=21</th>
<th>Phase 1–2</th>
<th>$P^{-1}$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>$-18.8 \pm 5.7%$</td>
<td>0.1155</td>
</tr>
<tr>
<td>PCO$_2$</td>
<td>$+16.3 \pm 10.9%$</td>
<td>0.4333</td>
</tr>
<tr>
<td>IOP</td>
<td>$+13.4 \pm 21.1%$</td>
<td>0.6568</td>
</tr>
<tr>
<td>Hg</td>
<td>$-49.7 \pm 7.8%$</td>
<td>0.7678</td>
</tr>
<tr>
<td>MAP</td>
<td>$-8 \pm 10.5%$</td>
<td>0.9574</td>
</tr>
<tr>
<td>Flow</td>
<td>$-32.1 \pm 14.5%$</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are registered as mean $\pm$ S.D. presenting their percentage difference between phases (middle column). Hg, hemoglobin; IOP, intraocular pressure; MAP, mean arterial pressure; n, number of patients; PCO$_2$, carbon dioxide arterial pressure; T, temperature. The level of significance was set at $P<0.05$.

4. Discussion

In general, the concept of regulation of blood flow in a vascular bed like the ONH is that systemic factors regulate the distribution of the cardiac output over the different vascular beds as a function of the hemodynamic situation of the whole body and that local factors (such as PO$_2$, PCO$_2$, pH, metabolic products) try to adapt flow to local needs [4].

Exceptionally, the brain, the retina and ONH, in contrast to other tissues, are controlled through a local autoregulatory mechanism in which the blood flow is regulated according to the metabolic needs and O$_2$ consumption demands despite moderate variations of perfusion pressure (PP) [5]. This can be achieved by changing the vascular resistance through alterations of the contractile state of arterioles and possibly of capillary pericytes. Since there is a limit to how far the terminal arterioles or capillaries can constrict or dilate, autoregulation operates only within a certain critical range of PP and breaks down when PP goes below or above this critical range. The ECC procedure, which is well-described as ‘surgical hypothermic controlled condition’, interferes with vascular tone by affecting the microcirculation through different homeostatic aspects derived from several hemodynamic modifications.

PP in the eye is determined as the local arterial blood pressure minus venous pressure. As venous pressure almost equals IOP, PP is defined as the difference between the mean ophthalmic artery blood pressure (MOAP) and the IOP. The MOAP is equal as $2/3$ of MAP, where $MAP=2/3 \left[ BP_{\text{diast}} + 1/3(BP_{\text{syst}} - BP_{\text{diast}}) \right]$. $BP_{\text{diast}}$ and $BP_{\text{syst}}$ are the brachial artery blood pressures during diastole and systole, respectively [6]. It is widely accepted that the autoregulatory mechanisms of tissue vascular beds like ONH remain functional when PP ranges approximately from 50 to 150 mmHg [5, 7]. According to our results, ONH blood flow is decreased from phase 1 to phase 2 by $32.1 \pm 14.5\%$ to a MAP reduction of $8 \pm 10.5\%$ and to an increase of IOP up to $13.4 \pm 21.1\%$ mmHg in comparison to baseline values. The decreased
values of MAP and the increased rate of IOP further reduced ONH PP below the critical limit of 50 mmHg leading us to the suspicion that ONH autoregulation could be abolished during cardiopulmonary bypass (CPB) (Fig. 5). Statistically, multivariate analysis showed no significant association between MAP and IOP with ONH blood flow despite the decrease of PP below this critical range. In general, cerebral autoregulation appears to be lost when PP is between 50 and 60 mmHg during CPB at moderate hypothermic operations [8, 9]. Assuming that the ONH circulation system behaves like that of the brain, similar autoregulatory perfusion changes could be recognized within ONH microcirculation during ECC.

Another important issue is the pH/PCO2 regulation during cardiovascular operations, which still constitutes a debatable topic. Apparently, there are two strategies for managing pH/PCO2 during hypothermic operations: the pH-stat and the α-stat. pH-stat opposes autoregulation through vasodilatation by the intraoperative preservation of PCO2 at higher values to correct pH. Blood flow is higher and pressure is passive and uncoupled from oxygen demand with pH-stat in contrary to α-stat in which blood flow is lower, autoregulated and coupled to oxygen demands. Although we use the pH-stat strategy to provoke vasodilatation as to increase flow rates [10], ONH blood flow was significantly decreased during ECC, implying that manipulation of PCO2 may have differing effects on ONH perfusion, IOP and on the coupling between flow and metabolism [11]. α-Stat seems a good alternative to maintain autoregulation but further decrease of ONH blood perfusion during hypothermia cannot be excluded.

What clearly influences ONH flow is whether the ECC procedure is prolonged or not. Our data suggest that the reduced ONH blood flow during on-pump moderate hypothermic cardiac operations is significantly associated with duration of CPB. In general, it is theorized that prolonged duration of CPB is strongly correlated with greater systemic inflammatory response and higher levels of endogenous catecholamines, indicators of increased vascular resistance [1]. Furthermore, data coming from current literature indicate that the duration of CPB is significantly longer in patients that developed ophthalmic manifestations like anterior ischemic optic neuropathy (AION) after heart surgery compared to those who were unaffected [1]. Additionally, prolongation of ECC time influences the regulation of significant physiological parameters including T, Hg concentrations, IOP, MAP and PCO2 [1]. Therefore, although not always attainable because of the severity of the underlying cardiac disease, the surgical strategy should include briefing in duration of ECC time.

The ideal temperature for uncomplicated adult cardiac surgery is an unsettled question [12]. Until recently nearly all operations reduced body temperature to 25–30 °C, similarly to our study, to protect the brain and increase the safe duration of circulatory arrest in case of emergency. On the other hand, hypothermia aggravates bleeding, increases systemic vascular resistance and lengthens duration of CPB [13]. Additionally, each degree centigrade reduction in body temperature is followed by a 6–7% decrease in cerebral blood flow [14]. Previous studies demonstrated a 48–62% decrease in cerebral blood flow during prolonged hypocarbic CPB procedures in canine models and this decrease persisted after the animal’s temperature was raised back to normal [11]. In our study, moderate hypothermia showed no direct interference on the decreased ONH blood flow. However, it remains one of the main predisposing factors for prolonged ECC. Perfusion at higher temperatures is lately recommended to avoid hypoperfusion phenomena and detrimental high blood temperatures during rewarming [15].

Finally, what should be the ideal hematocrit during CPB remains controversial because of competing advantages and disadvantages. Hypothermia reduces oxygen consumption and permits perfusion at 28 °C with hematocrits between 18% and 22%, but at higher temperature limits on-pump flow may not satisfy oxygen demands [12].

5. Limitations

Measurements expressed in absolute units cannot be performed by LDF. This device provides only relative blood flow data. This study is based on patients free of eye disease in order to exclude pathological backgrounds, which may affect the accuracy of our results. To study patients with eye disease, i.e. retinopathy, glaucoma or significant carotid disease, further investigations are needed in subjects classified according to their pathology.

6. Conclusion

The autoregulation of blood flow in a tissue vascular bed is defined as the ability of the tissue to maintain its blood flow relatively constant despite moderate variations of PP. It is legitimate to assume that ONH autoregulation can be abolished under circumstances of pH-stat regulation and decreased PP below 50 mmHg due to reduced MAP and
increased IOP within moderate hypothermic cardiovascular procedures. When this happens ONH blood flow decreases substantially. A positive association between ONH blood flow decrease and ECC time increase is also confirmed, thus it is of paramount importance to avoid ECC prolongation even in moderate hypothermic cardiovascular operations. Given that the retina-ONH circulation system is a part of the cerebral one, we infer that similar perfusion alterations even in moderate hypothermic cardiovascular operations. When this happens ONH blood flow decreases increased IOP within moderate hypothermic cardiovascular procedures. When this happens ONH blood flow decreases substantially. A positive association between ONH blood flow decrease and ECC time increase is also confirmed, thus it is of paramount importance to avoid ECC prolongation even in moderate hypothermic cardiovascular operations. Given that the retina-ONH circulation system is a part of the cerebral one, we infer that similar perfusion alterations even in moderate hypothermic cardiovascular operations. When this happens ONH blood flow decreases.

References


eComment: Optic nerve blood flow measurements during on-pump heart surgery

Authors: Georgios I. Tagarakis, University of Thessaly, Larissa, Greece; Fani Tsolaki, Vasiliki Trantou

doi:10.1510/icsvs.2010.260950A

The concept of the study by Nenekids et al. is interesting [1]. In a philosophical way of speaking, but also based on anatomic and physiological facts, the eye represents a window to the brain. Important findings regarding the ocular fundus can provide useful information concerning brain function and brain disorders. At this point, we would like to make a short remark in regard to the planning of the study. As a part or continuation of the study, we would probably be of some value to perform the same measurements to an analogous group of off-pump operated patients. This would show the exact impact of extracorporeal circulation to the reduction of the optic nerve blood flow in addition to other contributing parameters, such as the influence of the anaesthetic drugs’ regimen and intraoperative reduction of systemic blood pressure.

The issue of neurological disorders after heart surgery always remains of cardinal importance for the postoperative course of heart-operated patients.

Reference


eComment: Extracorporeal circulation and ocular/neurological status during heart surgery

Authors: Georgios I. Tagarakis, Department of Ophthalmology, Hippokration Hospital, Thessaloniki, Greece; Eleni Gogaki, Chrysanthi Lopatatzidi, Marios E. Daskalopoulos
doi:10.1510/icsvs.2010.260950B

Any innovative technical method that can contribute to the perioperative monitoring of cardiac operated patients is welcome and worthy of mention. We would like to address two practical issues to the authors regarding the mydriasis applied to the patients included in the study.

First of all, did the unilateral administration of tropicamide, which has an active period of four to eight hours, hinder in any way the neurological monitoring of the patients? Were other methods of neurological follow-up, such as intraoperative electroencephalogram, employed for this reason?

Second, tropicamide can cause a transient increase in intraocular pressure and thus a reduced flow to the supplying arteries of the optic nerve. This means that a fraction of the total reduction in optic nerve blood flow can be attributed to the aforementioned pharmacological interaction, in addition to the one caused as a result of extracorporeal circulation.

The above comments do not influence in any way the value and innovative character of the study by Nenekids et al. [1].

Reference


Response: Optic nerve blood flow measurements during cardiac surgery

Author: Nikolaos B. Tsilimigas, Department of Cardiovascular and Thoracic Surgery, University of Thessaly, Larissa, Greece
doi:10.1510/icsvs.2010.260950A

We would like to respond to the interesting comments made by Tsolaki et al. [1] and Tagarakis et al. [2], regarding our study [3] on optic nerve blood
flow during heart surgery under extracorporeal circulation (ECC). As on-pump surgery is believed to be more hazardous with regard to several categories of perioperative complications, we chose to study patients operated on with ECC. However, the idea of extending the study to include off-pump surgery is very creative and could be a future expansion of the current study. In relation to the effect of the mydriatic drug and the overall control of the patient’s neurological status, we have to say that intraoperative EEG monitoring as well as other methods of neurological diagnostics were applied or were at our disposal; as a result we consider the danger of false estimation due to the unilateral mydriasis to be extremely minimized.

References

