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Original Articles

Monitoring the Conjunctiva for Carbon Dioxide and Oxygen Tensions and pH During Cardiopulmonary Bypass

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Abstract: The purpose of this study was to measure, for the first time, multiple physiologic parameters of perfusion (pH, PCO_2, PO_2, and temperature) from the conjunctiva of adult patients during cardiopulmonary bypass while undergoing cardiothoracic surgery. Ten patients who underwent either intracardiac valve repair, atrial septal defect repair, or coronary artery bypass graft surgery had placement of a sensor which directly measured pH, PCO_2, PO_2, and temperature from the conjunctiva. Data were stratified into seven phases (0–5 minutes prior to bypass; 0–5, 6–10, and 11–15 minutes after initiation of bypass; 0–5 minutes prior to conclusion of bypass; and 0–5 and 6–10 minutes after bypass) and analyzed using a mixed model analysis. The change in conjunctival pH over the course of measurement was not statistically significant ($p = .56$). The PCO_2 level followed a quadratic pattern, decreasing from a mean pre-bypass level of 37.7 mmHg at baseline prior to the initiation of cardiopulmonary bypass to a nadir of 33.2 mmHg, then increasing to a high of 39.4 mmHg at 6–10 minutes post bypass ($p < .01$). The PO_2 declined from a mean pre-bypass level of 79.5 mmHg to 31.3 mmHg by 6–10 minutes post bypass and even post-bypass, it never returned to baseline values ($p < .01$). Temperature followed a pattern similar to PCO_2 by returning to baseline levels as the patient was re-warmed following bypass ($p < .01$). There was no evidence of any eye injury or inflammation following the removal of the sensor. In the subjects studied, the conjunctival sensor yielded reproducible measurements during the various phases of cardiopulmonary bypass without ocular injury. Further study is necessary to determine the role of conjunctival measurements in critical settings.
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Upwards of 6% of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) suffer adverse neurologic outcomes (1). Efforts to measure the perfusion to the brain during surgery are cumbersome and inefficient. This study used the unique gas permeable properties of the conjunctiva of the eye to measure pH, carbon dioxide, and oxygen tensions as well as temperature of the conjunctiva during cardiac surgery. Since the conjunctiva's circulation arises from branches of the carotid artery, as does the retinal vessels, conjunctival pH, carbon dioxide tension, and oxygen tension could be a surrogate for the perfusion of the retina and by extension even of the brain.

Perfusion of other tissues has been assessed by measuring pH, partial pressure of carbon dioxide, and/or partial pressure of oxygen. There have been studies on the use of gastric tonometry to measure perfusion to the gut (2), ways to measure bladder perfusion (3), and attempts made to use noninvasive cerebral oximetry to measure cerebral perfusion following head injury (4). Although, some of these measurements can be used clinically, none have yet become standard of care in the operating room or intensive care unit.

Attempts at conjunctival monitoring have been performed in the past, but are not currently clinically used. The original conjunctival sensor was similar to a large

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contact lens, required precise placement in the eye, and only measured oxygen tension (5). Nevertheless, it proved useful in several clinical situations (6–8).

Recently, new technological developments have permitted pH and carbon dioxide tension to be readily measured in addition to that of oxygen (9,10). The sensor used in this study has been reduced to a .5 mm diameter soft polyethylene coated wire that can conform to the contour of the conjunctival fornix of the eye, is relatively easy to place, and requires only the distal 2 cm of the sensor to be in contact with the conjunctiva. This study was conducted to assess the feasibility of such monitoring in adult humans undergoing cardiac surgery as cardiac surgery and CPB engender numerous physiologic changes which permit assessment of the ability of the conjunctival sensor to respond to such changes.

MATERIALS AND METHODS

The Human Subjects Protection Committee of the Los Angeles Biomedical Foundation at the Harbor – UCLA Medical Center approved this study for patients exceeding 18 years of age undergoing general anesthesia for procedures expected to last at least 4 hours. Study consent was obtained during the pre–operative visit. This work was Health Insurance Portability and Accountability Act compliant and adhered to the tenets of the Declaration of Helsinki. Patients who had previous eye surgery or a history of ocular injury were excluded. The study was initially approved to allow for 4 hours of continuous use; after the first two patients, the protocol was modified to allow 6 hours of continuous use.

The monitoring system (Paratrend 7+, Diametrics Medical Systems, Bucks, UK) consisted of a sterile sensor which extended at least 2 cm in contact with the conjunctival membrane, a monitor to display the measured values, and a device for calibrating the sensor prior to use. The sensor consisted of a thin flexible polyethylene tube with a diameter <.5 mm which measured pH and carbon dioxide using the principal of optical absorption and changes in phenol red dye determined by absorbance changes of green versus red fiber-optic light. Oxygen values were measured using the principle of fluorescence quenching by using blue light (465 nm). Temperature was measured with a thermocouple of copper and nickel alloy wire which generated a temperature dependent voltage. All measurements were then transmitted via appropriate cables to the monitor for display. The sensor is capable of responding to changes in the parameters measured in less than 6 seconds.

The sensor was calibrated, prior to insertion, by placing it into a chamber to allow the calibration gases to flow past it. A three point calibration process, using gases with fixed concentrations of carbon dioxide and oxygen that are supplied by the manufacturer, was used to ensure sensor function over the range of physiologic values. This process lasted for 31 minutes and was automatic once initiated. This process was able to be performed well before the initiation of CPB, as the sensor, once calibrated, could be used up to 12 hours later. Using an 18 gauge Jelco Strip Intravenous Catheter (Johnson & Johnson, Arlington, TX) attached to the corner of the eye, the sensor was advanced through the catheter into contact with the conjunctiva in the lower fornix (Figure 1). The eye was then taped shut. Data were stored on an attached laptop computer.

Prior to the insertion of the sensor, the eyes were examined with a portable slit-lamp (Kowa Optimed Incorporated, Japan) for any abnormalities. The examination was repeated following sensor removal. The sensor was removed at the completion of the surgery.

The values for pH, partial pressures of oxygen and carbon dioxide, and temperature were electronically recorded every minute for the duration of the surgery. Ten patients were studied who underwent cardiac surgery requiring use of CPB. Eight underwent coronary artery bypass graft surgery, one had an aortic valve replacement, and one underwent an atrial septal defect repair. The mean age of these patients was 56.2 ± 8.5 years with a range of 38–72 years.

Statistical Model

The data were analyzed using mixed model analyses (11) appropriate for analysis of longitudinal data with multiple factors, using package nlme for mixed effects models (12) in R version 2.4.1 (13). In such analyses, each subject effectively provides his/her own baseline. To determine the sensitivity of the conjunctival sensor to

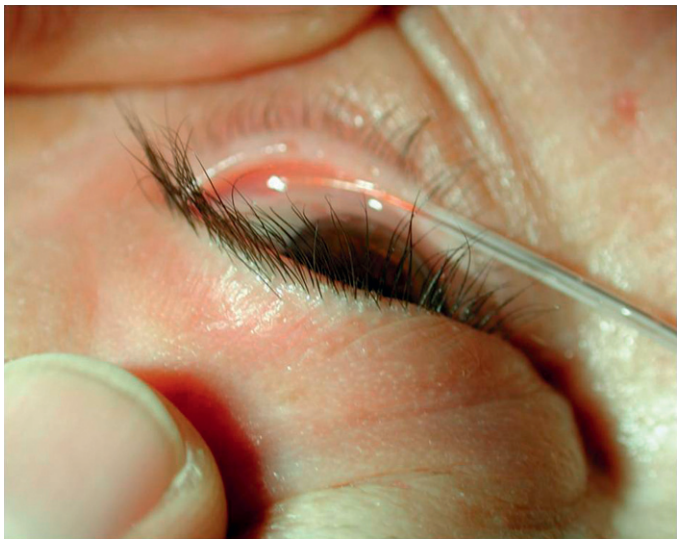

Figure 1. Photograph of sensor inserted and resting on the conjunctiva of one of the subjects.

the changes occurring during cardiac surgery, the data for pH, partial pressure of carbon dioxide, partial pressure of oxygen, and temperature were divided into the following seven phases:

1. The five minutes prior to bypass
2. The initial five minutes on bypass
3. Minutes 6–10 on bypass
4. Minutes 11–15 on bypass
5. The last five minutes on bypass
6. The first five minutes off bypass
7. Minutes 6–10 off bypass

These seven phases were chosen to indicate values just prior to bypass, representative values at the beginning and end of the period on bypass, and changes in parameters that occurred after bypass was terminated. This type of analysis permitted uniformity of physiological changes while avoiding the variable duration of the middle period of bypass. These seven phases were expected to be clinically similar for all patients since clinical care was well standardized during these periods. This would allow better comparisons of the conjunctival readings. The mixed effects model enabled analyses of the stability of data within each phase and to determine if the comparisons between phases were valid. The model accounted for the different baseline measurements for each patient. It also allowed comparisons of the changes from each baseline. Additionally, the model accounted for missing data without affecting the statistical significance of any comparisons.

RESULTS

The 10 patients were monitored for a total of 38.5 hours (range 2 hours 13 minutes to 5 hours 15 minutes). Mean bypass time was 131 minutes with a range of 48–166 minutes. Upon removal of the sensor, no subject demonstrated injection of the conjunctiva or any other ocular abnormality. Mean values for the four variables over the seven time periods are shown in Table 1.

Conjunctival pH measurements changed only slightly during monitoring. During each phase, the values were stable, with no significant fluctuations ($p = .61$). The baseline value, prior to going on bypass, was 7.03, and the same value was measured during the last 5 minutes of CPB. At the phase of 6–10 minutes following bypass completion, the value was 7.05. The overall pH change during the monitoring period was –.01 ($p = .56$) (Figure 2A).

Conjunctival carbon dioxide values changed significantly. The initial mean PCO_2 value was 37.2 ± 7.2 mmHg. The period of 11–15 minutes on bypass was the lowest for CO_2 values, 33.3 ± 3.9 mmHg. The most significant phase change for carbon dioxide was from the 11–15 minutes of CPB period to the last five minutes off bypass during

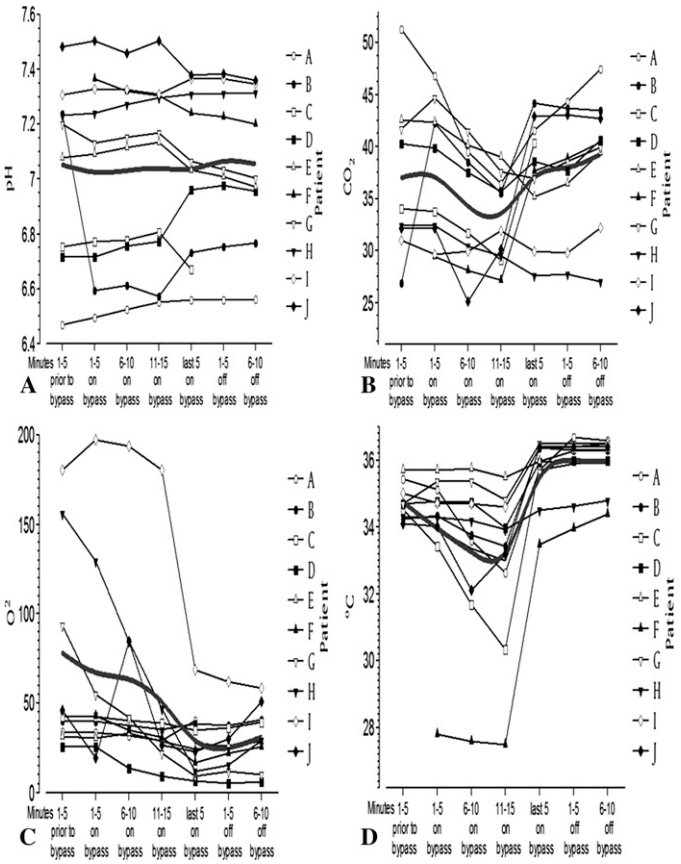

Figure 2. Measurements of pH (A), PCO_2 (B), PO_2 (C), and temperature (D) from the conjunctiva of patients undergoing cardiac surgery. Heavy line = spine fit representing group average.

Table 1. Mean (±SD) of pH, PCO_2, PO_2, and temperature values by study phase.

Phase Number	Phase Description	pH	PCO_2 (mmHg)	PO_2 (mmHg)	Temp (°C)
Phase 1	Five minutes prior to bypass	7.03 ± 0.33	37.2 ± 7.2	79.4 ± 57.6	34.8 ± 0.6
Phase 2	Initial five minutes on bypass	7.02 ± 0.34	37.3 ± 6.3	66.4 ± 57.2	33.9 ± 2.2
Phase 3	Minutes 6–10 on bypass	7.03 ± 0.31	34.3 ± 5.6	63.9 ± 52.7	33.4 ± 2.3
Phase 4	Minutes 11–15 on bypass	7.04 ± 0.32	33.3 ± 3.9	51.5 ± 52.4	33.0 ± 2.3
Phase 5	Last 5 minutes on bypass	7.03 ± 0.29	37.5 ± 5.1	28.0 ± 21.1	35.7 ± 0.9
Phase 6	Initial 5 minutes off bypass	7.07 ± 0.27	37.8 ± 5.6	25.6 ± 16.1	35.9 ± 0.9
Phase 7	Minutes 6–10 off bypass	7.05 ± 0.26	39.3 ± 5.9	31.3 ± 17.3	36.0 ± 0.8

which carbon dioxide rose by 4.3 mmHg to 37.5 ($p < .01$). Carbon dioxide reached its highest value during the last phase (6–10 minutes after bypass), 39.4 ± 0.8. Each change of phase resulted in statistically significant changes in the carbon dioxide measurement ($p < .01$). However, the carbon dioxide values did not fluctuate within time periods ($p = .41$). The plot of the carbon dioxide tension values is V-shaped, demonstrating the decline in levels during bypass and the rapid increase in the tension once pulsatile flow was restored and the conclusion of bypass (Figure 2B).

Oxygen showed the most variation of the parameters studied (Figure 2C). Bypass caused a statistically significant decline in oxygen values ($p < .01$). During the period of 6–10 minutes following bypass, the mean oxygen value (31.2 mmHg) was 60.7% lower than the baseline pre-bypass, 79.4 mmHg. Oxygen values showed no intra-phase effect – the values were stable during each of the seven time periods analyzed. Oxygen declined linearly with time ($p < .01$). Once bypass was initiated the values fell and never returned to baseline. Even when outlier values that did not fit linearly were taken into account, time was still a statistically significant factor for the changes in oxygen.

Temperature showed a quadratic relationship ($p < .01$) with the phase of 11–15 minutes on bypass showing the lowest mean value, 33.0°C ± 0.2 (Figure 2D). The lowest value recorded during this phase was 27.5°C. Almost all patients re-warmed to 36.0° ± 0.8 during the 6–10 minutes following bypass. No patient underwent deep hypothermic circulatory arrest. The temperature values were normalized to 37°C (alpha stat).

During surgery, the aorta was sometimes cross-clamped. Within 1 minute, the conjunctival oxygen tension fell to 0 and the CO_2 level rose. They returned to their previous values 2 minutes after the cross-clamping was completed. Also noteworthy was the response to transfused blood during the surgery. Within 2 minutes of transfusion, conjunctival pH began to decrease, carbon dioxide tension rose, and oxygen tension fell.

DISCUSSION

This study is the first to monitor gas exchange of oxygen and carbon dioxide across the conjunctiva in humans. We chose to study patients during cardiac surgery because CPB can cause many unique physiologic responses secondary to changes in perfusion and systemic blood pressure which may affect the conjunctival circulation. Our data demonstrate that the sensor was responsive to the initiation and termination of CPB, as well as activity during the procedure such as blood transfusion and cross-clamping of the aorta. All patients had a similar, statistically significant, response, as measured by the sensor, to the phases of CPB (Figure 2).

In most intensive care units, the status of oxygen saturation is measured with a pulse oximeter. Pulse oximetry, however, is limited since it is based on oxygen saturation. Hemoglobin is fully saturated at PaO_2 levels above approximately 90 mmHg, thus pulse oximetry is completely insensitive to the higher oxygen tensions. Pulse oximetry is also dependent on adequate perfusion and is affected by temperature changes, ambient light, and motion artifact. Response time to changes in oxygenation can be variable as well (14).

The conjunctiva is an externally available permeable membrane by which to measure gas perfusion. The conjunctival sensor has only the very thin epithelium between it and the capillaries, perhaps yielding a more accurate assessment of the variables measured from the tissue. On the other hand, skin has a keratin layer which interferes with the accuracy of transcutaneous measurements of oxygen and carbon dioxide.

During CPB, we determined that conjunctival pH remained essentially constant. This is consistent with the findings in other studies that pH is relatively fixed and well buffered in general tissue, and would require very large persistent physiologic perturbations to change (15). This did not occur in our patients. The changes caused by the various interventions during the surgical procedure tended to be rapid and short lived. Studies of the effect on brain and tissue metabolism of normothermic cardiopulmonary bypass (as used in our study) did not change high energy phosphate levels or intracellular pH (16). The earliest report of conjunctival pH noted that the conjunctival pH was generally .2 pH units lower than the arterial value (17). As can be seen from Figure 2A, the initial range of conjunctival pH in our study was 6.5–7.5, with clear modulation of the values across the study period, as would be expected in an *in-vivo* model. It is unclear why three of the subjects had initial pH values <7.0, nor is it clear if the .2 unit gradient noted applies in all clinical circumstances. Nevertheless, the overall change in pH values between each of the phases or across the study period was not significant.

Conjunctival carbon dioxide tension did change significantly during testing. One study of gastric luminal PCO_2 during CPB demonstrated declining values initially, and, similar to our findings, an increase upon the restoration of pulsatile flow (18). These authors attributed this finding to the increasing acidosis in tissues that are not perfused. Once perfusion is restored, the cellular buffering system causes a rise in carbon dioxide tension. Hence, increased tissue carbon dioxide measurements may indicate impaired flow. This may explain the elevation of conjunctival PCO_2 seen after the restoration of pulsatile flow in our patients.

Conjunctival oxygen tension declined steadily during the bypass procedure. A prior investigation which measured muscle gastric mucosal oxygen levels during

CPB showed that tissue oxygenation fell sharply during the initiation of cardiopulmonary bypass and remained significantly below baseline for 3 to 5 hours following the procedure (19). These investigators did not find any relationship between arterial blood gas levels and the tissue pH or oxygen tension. Our findings of a significant conjunctival oxygen tension decrease during bypass are consistent with these results. The graphical depiction of their data is almost identical to our decrease in conjunctival oxygen during bypass. Our protocol did not permit us to continue monitoring long enough to determine the time needed for the values to return to baseline.

Measuring the oxygen tension of brain tissue to help care for stroke patients has been suggested (20). Near-infrared spectroscopy to monitor tissue oxygen tension of patients following severe head injury or subarachnoid hemorrhage has been attempted with some success (21). Cerebral oximetry has also been used to monitor cerebral perfusion following severe head injury (4). As well, near-infrared spectroscopy has been introduced into the cardiac operating room. Although, changes in the regional oxygen saturation (rSO_2) have been correlated with neurologic events during surgery, embolic events and infarcts affecting the basilar areas of the brain do not seem to engender rSO_2 drops that would warn the clinician of the potential for adverse events (22).

Conjunctival temperature followed a quadratic curve, similar to carbon dioxide. The lowest temperature recorded was during the last phase of bypass prior to re-warming with a gradual increase toward baseline as the patient came off bypass. A prior study of conjunctival temperature showed that the temperature not returning to baseline could be a marker for poor outcome (23). As none of our patients underwent cardiac arrest or became severely hypotensive, we cannot confirm this finding.

The conjunctiva has been previously used for the monitoring of oxygen tension only (5). These studies were informative in a variety of clinical situations, including the emergency room (6), during helicopter transport (7), in diabetes mellitus (24), sickle cell disease (25), neonates (8), and the aged (26). Since then, there have been only a few papers about the use of conjunctival monitoring. One report did show that the conjunctival carbon dioxide sensor measurements were shown to correlate well with arterial PCO_2 in respiratory acidosis and alkalosis in a canine model (27). Another study determined that the conjunctival oxygen tension/arterial oxygen tension index correlated well to cerebral blood flow as measured by positron emission tomography in healthy adult volunteers (28). More recently, an analysis of conjunctival blood flow using an intravital microscope showed the responsiveness of conjunctival vasculature in an animal hemorrhage model (29).

While a few studies have questioned the use of conjunctival oxygen readings (30–32), others have found a role for conjunctival monitoring in pulmonary surgery and in resuscitation from shock (33–35). A possible role for conjunctival oxygen monitoring during cardiopulmonary resuscitation to help determine prognosis for recovery has also been described (36).

The technology demonstrated here could have multiple potential uses. One area of application, in addition to cardiothoracic surgery, could be the neonatal intensive care unit, as an adjunct to reduce the incidence of retinopathy of prematurity and cerebral palsy. Recent investigations have clarified that better control of blood gases, especially oxygen, can impact retinopathy of prematurity and cerebral palsy. Tin and associates found that neonates with oxygen supplemented to a range of 88–98% (as determined by pulse oximetry) were four times as likely to need retinal cryotherapy as newborns who maintained a level of 70–90% (37). The incidence of cerebral palsy was similar between the two groups. A strict oxygen administration policy can reduce the retinopathy incidence from 12.5 to 2.5% over a 4-year period (38). This more rigorous policy included minimizing repeated episodes of alternating hypoxia/hyperoxia, and avoiding episodes of high oxygen saturation levels. Fluctuating oxygen tensions in very low birth weight infants have been linked to a higher risk of threshold retinopathy of prematurity (39). These and similar studies suggest that, perhaps, the more precise measurements provided by a conjunctival monitor measuring oxygen tension, as well as carbon dioxide tension, pH, and temperature, might enable even better outcomes.

We undertook this study to determine if measuring the pH, carbon dioxide, and oxygen diffusing across the conjunctival membrane is possible and safe. The analysis of these data shows that the conjunctival sensor as used in this study detected changes during the different phases of cardiac surgery in adults undergoing cardiopulmonary bypass. The data presented here encourage us to pursue further development of the sensor and to determine the applicability of the technology to various clinical realms, which could include the emergency department, the operating room, and the intensive care units.

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