NIRS-Based Quantitative Measurement of Autoregulatory Effects on Microvascular Hemoglobin Oxygenation: Assessment of Differences between Non-Diabetics and Type II Diabetic Subjects

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ABSTRACT

By examining the simultaneous evolution of oxyhemoglobin (Hb_{oxy}) and deoxyhemoglobin (Hb_{deoxy}) in NIRS image time series, we have derived indices of the competency of autoregulation. Applying these measures to data collected from the forearms of type II diabetics and normal subjects reveals statistically significant differences between the two patient populations. While some of the analyses involve application of a transient ischemia protocol, others consider only data collected during a resting condition.

OCIS codes: (100.6950) Tomographic imaging processing; (100.6890) Three-dimensional image processing; (120.3890) Medical optics instrumentation.

INTRODUCTION

Importance of tissue autoregulation
- tissues maintain oxygen balance
- vital organs depend largely on autoregulation for the maintenance of homeostasis
  - e.g, brain, heart, kidney, skeletal muscle
- Impairment can drive tissues into oxygen debt
  - ratio of Hboxy to Hbdeoxy will be altered
    - sufficiently severe alteration will adversely affect metabolism and homeostasis
  - drugs (e.g., nicardipine, remifentanyl, propofol, isoflurane, etc.), hormones (e.g., aldosterone, angiotensin, nitric oxide), metabolism, pressure, posture, and various disease states, all affect tissue oxygenation by altering autoregulation
    - autoregulation is impaired in patients with cardiovascular disease [1]

Challenging task: devise a portable and reproducible technique capable of delineating subtle differences in the time- and position-dependent concentrations of Hb_{oxy} and Hb_{deoxy}.
- functional diffuse optical tomography (fDOT) technique [2]
  - is safe, effective, portable, requires no skill on the part of the patient, and accurate in quantifying the level of Hb_{oxy}, Hb_{deoxy} and total Hb in tissues
  - we have devised a data analysis strategy that yields information about tissue microvascular autoregulation

Patients with type-II diabetes mellitus (DM2):
- have impaired macrovascular and microvascular myogenic responsiveness
  - can ultimately lead to vascular hypertrophy [3]
- The hypertrophy can affect autoregulation adversely, and disturb the balance between Hb_{oxy} and Hb_{deoxy}.
- Accordingly, we expect that our autoregulatory-state (ARS) analysis will be able to accurately delineate differences in these parameters, when cohorts of healthy control (HC) subjects and patients with DM2 are compared.
- Here we present the results of such a study, which considered fDOT data collected from the forearms of 37 study participants
  - 14 with DM2, 23 HC
  - age- and gender-matched

METHODS

fDOT measurements:
- multi-channel, continuous wave, near infrared imager (NIRx Medical Technologies)
- simultaneous dual-wavelength (760nm and 830nm) measurement
- ring-shaped measuring head (Figure 1)
  - contains 24 evenly spaced optical fibers
  - placed on the subject's left forearm
  - each fiber acts as both a source and a detector → total of 576 measurement channels
- image data acquisition rate = 2.2 Hz (i.e., 1 time frame = 0.45 s)

fDOT scan (Figure 2):
- starts with a baseline period of 1400-1500 time frames (~11 minutes) duration
- followed by rapid inflation of a blood pressure cuff placed about the subject's left arm
  - maximum pressure is 180 mmHg, > systolic blood pressure in almost all subjects
    - produces arterial ischemia
  - cuff is left inflated for 400 time frames (~3 minutes), then rapidly deflated
- measurement is continued for another ~2200 time frames (~17 minutes)
  - subjects' fDOT responses typically exhibit an episode of reactive hyperemia, followed by a apparent return to baseline

Data processing and analysis:
- optical data are low-pass filtered and normalized to a resting-baseline mean value
- images of ΔHb_{oxy} and ΔHb_{deoxy} concentrations are computed, using a first-order perturbation algorithm [4].
- six ARS are defined (see Table 1), according to the algebraic signs of ΔHb_{oxy}, ΔHb_{deoxy}, and their sum $\Delta Hb_{total} = \Delta Hb_{oxy} + \Delta Hb_{deoxy}$
  - each relational category reasonably corresponds to a different underlying state of oxygen supply/demand balance or imbalance
- for analysis of data in the baseline and post-recovery resting phases, twelve plausible metrics of autoregulatory competence (see Figure 3, Table 2) are considered.
- nonparametric (Mann-Whitney U) tests were performed to determine which of the metrics revealed significant differences between the HC and DM2 subject groups.

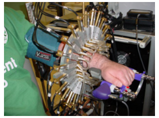

Figure 1. Placement of the fDOT measuring head and blood-pressure cuff, about a study subject's left forearm and left arm, respectively.

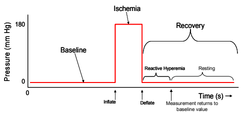

Figure 2. Schematic of the time course of the measurement protocol. Nomenclature adopted for the different segments of the measurement cycle is indicated.

Hb State	State 1	State 2	State 3	State 4	State 5	State 6
Hb_{oxy}	-	-	-	+	+	+
Hb_{deoxy}	-	+	+	+	-	-
Hb_{total}	-	-	+	+	+	-
Table 1	Balanced	Uncom-pensated O_2 debt	Compen-sated O_2 debt	Balanced	Uncom-pensated O_2 excess	Compen-sated O_2 excess

Definitions of the six autoregulatory states (ARS), in terms of the algebraic signs (wrt baseline mean values) of the Hb concentrations. Bottom row gives a plausible physiological interpretation for each ARS.

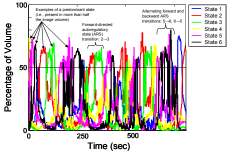

Figure 3. Definitions for "predominant ARS," "forward-directed transition," and "backward-directed transition."

Metric Number	Metric Description
1	Percentage of time interval having a predominant state
2	Number of distinct sub-intervals having a predominant state
3	Mean duration of a predominant state
4	Standard deviation of predominant-state durations
5	Number of $N \to N$ predominant-state transitions (N = 1, 2, 3, 4, 5 or 6)
6	Number of ambiguous (i.e., $N \to N \pm 3$) predominant-state transitions
7	Number of forward-directed (i.e., $N \to N$+1 or $N \to N$+2) predominant-state transitions
8	Number of backward-directed (i.e., $N \to N$-1 or $N \to N$-2) predominant-state transitions
9	Mean value of forward-directed transition step-size
10	Standard deviation of the forward-directed transition step-size
11	Mean value of the of the backward-directed transition step-size
12	Standard deviation of the of the backward-directed transition step-size

Table 2. Twelve scalar metrics computed from the baseline-period and resting-period data for each study subject. These were subsequently tested for their effectiveness as predictors of diabetes (retrospective study).

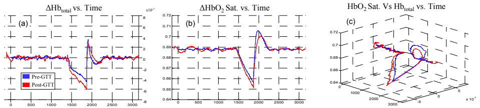

Figure 4. Time courses of the total Hb perturbation (a), and the Hb O_2 saturation (b), in the forearm of a selected study subject. (c) - Combining the ΔHb_{tot} and HbO_2Sat data into a single 3D curve plot yields an estimate of time-varying supply-demand balance.

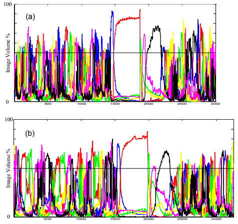

Figure 5. Time courses of volume fraction for each ARS, for the same study subject as in Fig. 4, prior (a) and subsequent to (b) the glucose tolerance test.

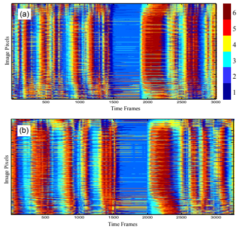

Figure 6. Time courses of the ARS in every image pixel, for the same study subject as in Fig. 4, before (a) and after (b) the GTT.

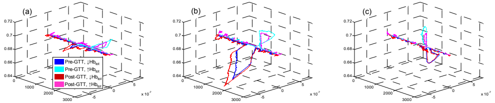

Figure 7. 3D plots of ΔHb_{tot} vs. HbO_2Sat vs. time, for the same study subject as in Fig. 4, with the original image time series resolved into their ARS components. (a) – ARS 1 and 4 (balanced); (b) – ARS 2 and 5 (uncompensated oxygen debt, uncompensated oxygen excess); (c) – ARS 3 and 6 (compensated oxygen debt, compensated oxygen excess).

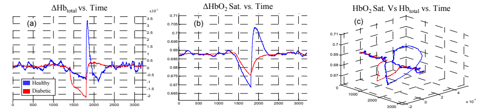

Figure 8. Time courses of (a) - ΔHb_{tot}, (b) - HbO_2Sat, in the forearms of age-matched HC and DM2 study subjects. (c) – 3D plot of ΔHb_{tot} vs. HbO_2Sat vs. time, provides an estimate of time-varying supply-demand balance.

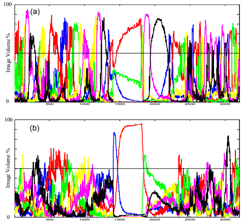

Figure 9. Time courses of volume fraction for each ARS, for the same pair of study subjects as in Fig. 8. (a) – HC, (b) – DM2.

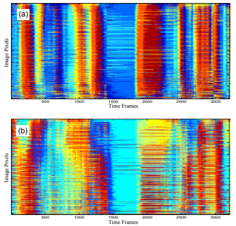

Figure 10. Time courses of the ARS in every image pixel, for the same pair of study subjects as in Fig. 8. (a) – HC, (b) – DM2.

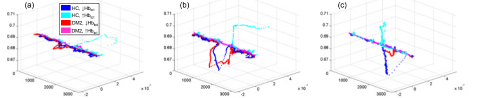

Figure 11. 3D plots of ΔHb_{tot} vs. HbO_2Sat vs. time, for the same study subjects as in Fig. 8, with the original image time series resolved into their ARS components. (a) – ARS 1 and 4 (balanced); (b) – ARS 2 and 5 (uncompensated oxygen debt, uncompensated oxygen excess); (c) – ARS 3 and 6 (compensated oxygen debt, compensated oxygen excess).

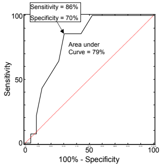

Figure 12. ROC curve for one of the ARS-based metrics (#7 in Table 2, for the resting segment of the image time series) that shows a statistically significant difference between the HC and DM2 subjects.

Metric	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Area under Curve (%)
#8, baseline segment	71	57	50	76	70
#2, resting segment	64	87	75	80	77
#7, resting segment	86	70	63	89	79
#8, resting segment	71	78	67	82	79

Table 3. Diagnostic accuracy parameters for the four ARS-based metrics that show a statistically significant difference between the HC and DM2 sub-groups.

RESULTS

Exemplary case 1 (Figures 4-7):
- Subject is a healthy control (HC)
  - female, 32 years old, BMI = 24.5
- Underwent two fDOT measurement cycles
  - before a glucose tolerance test (GTT)
  - after drinking the GTT beverage
- Conventional presentation modes for fDOT results reveal some indications of altered vascular responsiveness as a consequence of the glucose challenge
  - reactive hyperemia has lower peak amplitude, and takes longer to develop, post-GTT (Fig. 4(b))
- However, the *apparent* result is that the dynamics are essentially identical during the baseline in both cases, and quickly recover to baseline after ischemia is terminated
  - Baseline and resting periods seemingly are indistinguishable
- Time courses of the ARS volume fractions (Fig. 5) and the evolution among ARS in individual pixels (Fig. 6) reveal differences not only in the reactive hyperemia phase of the experiment, but also during baseline
  - e.g., predominant ARS states have appreciably longer average duration after the GTT than before
  - e.g., baseline- and resting-phase dynamics are more similar to each other before GTT than after
- Resolving the 3D ΔHb_{tot} vs. HbO_2Sat vs. time curves into their ARS components (Fig. 7) likewise yields greater insight into the competence of supply-demand balance
  - After the GTT, the subject:
    - develops a greater degree of uncompensated oxygen debt during ischemia (Fig. 7(b)),
    - is less capable of increasing blood supply to meet the demand following release of the ischemia (Fig. 7(b),(c)).

Exemplary case 2 (Figures 8-11):
- Two subjects
  - One subject is a healthy control: female, 51 years old, BMI = 21.0
  - Second subject has DM2: female, 57 years old, BMI = 35.0
- Conventional presentation for fDOT results (Fig. 8) reveal a gross difference between the subjects' responses to ischemia
  - reactive hyperemia is basically absent in the DM2 subject (Fig. 8(a),(b))
- Appreciably lower temporal variability also is seen in the baseline- and resting-phase data for the DM2 subject. However, there is little evidence of gross differences between vascular dynamics during the baseline and resting phases
- ARS volume fraction plots (Fig. 9) for these two subjects show that:
  - Subject with DM2 has many fewer instances of a predominant ARS state.
  - The maximum volume fraction achieved is substantially lower for the DM2 subject
  - DM2 subject also experiences an appreciably higher degree of uncompensated oxygen debt during ischemia
- ARS vs. time for individual pixels (Fig. 10) reveals a higher degree of spatial coordination in the HC subject

- ARS-resolved 3D plots of ΔHb_{tot} vs. HbO_2Sat vs. time (Fig. 11) indicate that, for the subject with DM2, it is difficult to impossible for the vasculature to modulate supply in response to fluctuations in demand
- We hypothesize that vasculopathies associated with DM2 are the principal determinant of the observed differences. We predict that:
  - a similar comparison between two HC subjects, having the same age and BMI differences as seen here, would show a smaller effect size for those factors
  - a similar comparison between HC and DM2 subjects who are perfectly age- and BMI-matched, would reveal an effect size for DM2 almost as large as in the example presented here
  - Statistically significant ARS-based group differences will be found between sets of HC and DM2 subjects

Preliminary clinical study
- Two subject groups were included
  - Healthy controls (N_1 = 23)
    - 10 male, 13 female
    - Age: mean = 57.0 years, SD = 7.3 years
    - BMI: mean = 32.1, SD = 7.0
  - Type II diabetes (N_2 = 14)
    - 7 male, 7 female
    - Age: mean = 59.8 years, SD = 9.3 years
    - BMI (one missing value): mean = 32.5, SD = 3.3
- Values for the 12 scalar metrics outlined in Table 2 were computed for each subject, for both the baseline and resting segments of the image time series.
  - i.e., a total of 24 candidate metrics
- Differences between the groups were assessed using the Mann-Whitney U test.
  - Statistically significant group differences were found for 4 metrics:
    - Baseline segment: Number of backward-directed predominant-state transitions
    - Resting segment: Number of sub-intervals having a predominant ARS state
    - Resting segment: Number of forward-directed predominant-state transitions
      - Corresponding receiver operator characteristic (ROC) curve [5] is shown in Figure 12
      - ROC curves for the other 3 are similar
    - Resting segment: Number of backward-directed predominant-state transitions
  - Diagnostic accuracy parameters—sensitivity, specificity, positive and negative predictive values, and area under the ROC curve—for the four metrics are listed in Table 3.

CONCLUSIONS

- The diabetic subjects we examined tend to show a reduced reactive hyperemia response following an episode of induced ischemia. But aside from this obvious effect, in conventional fDOT time series data it is difficult to detect differences between results for diabetic and non-diabetic subjects, or intra-subject differences between the pre- and post-ischemia epochs
- In contrast, patients with DM2 show a markedly different *autoregulatory profile* when compared to non-diabetics. This difference, while observable even in an unstressed baseline condition, is even more apparent following an applied stress such as increased oxygen demand or decreased blood supply.
- By resolving fDOT image time series into the six autoregulatory states described in this and accompanying presentations, we can discern large and previously undetected differences between the pre- and post-ischemic conditions within an individual, between metabolically stressed and unstressed conditions within an individual, and between subjects with and without Type II diabetes.

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