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Monitoring fluid responsiveness using hybrid diffuse optics during passive leg raising maneuver

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Abstract: Fluid therapy is essential in hemodynamic resuscitation, but not all patients benefit. Passive leg raising predicts fluid responsiveness, necessitating reliable cardiac output (CO) monitoring. Here, we present a complementary approach using hybrid diffuse optics as a surrogate for CO monitoring. © 2025 The Author(s)

Introduction

Fluid therapy plays a key role in hemodynamic resuscitation, which aims to restore blood perfusion and ensure adequate oxygen delivery to tissues, especially in critically ill patients. However, not all patients benefit from it, making it essential to identify those who will respond to minimize potential adverse outcomes. Fluid responsiveness is defined as a patient's ability to increase cardiac output (CO) following intravenous fluid administration. In the intensive care (ICU), the gold standard assessment for fluid responsiveness involves performing a challenge that mimics the administration of fluids and measuring the resulting variations in CO. Passive leg raising (PLR) is a well-established and reliable bedside technique that simulates a fluid infusion by transiently increasing venous return [1], allowing clinicians to predict fluid responsiveness without administering fluids [1]. An increase in CO of more than 10% during PLR suggests fluid responsiveness, but this response is dynamic and may change over time. In conditions such as septic shock, transient CO changes can diminish within a minute, highlighting the need for continuous, real-time CO monitoring to guide fluid management effectively. Despite this need, achieving reliable CO monitoring in the ICU remains a complex task. Invasive techniques, such as thermodilution using a pulmonary artery catheter, provide accurate CO measurements but pose risks of severe complications. Pulse Contour Cardiac Output (PiCCO) offers a less invasive alternative by combining pulse wave analysis with transpulmonary thermodilution, though it requires frequent recalibration. Minimally invasive systems like ProAQT/PulsioFlex (Getinge, Sweden) estimate CO using arterial waveform analysis and biometric data, but their accuracy is limited in patients receiving vasopressors [2,3].

In this work, we propose a non-invasive optical approach for monitoring changes in CO during a PLR challenge. This approach utilizes a state-of-the-art hybrid diffuse optical platform ("hDOS" [4]), which integrates time-domain and diffuse correlation spectroscopies to assess hemodynamic changes in both healthy subjects and critically ill patients. By providing a real-time, non-invasive complementary approach to traditional CO monitoring methods, this technique enables a more direct assessment of tissue perfusion and oxygenation.

Methods

We monitored fluid responsiveness during a PLR maneuver in twenty-three healthy subjects and thirteen general ICU patients (including septic and non-septic) using the "hDOS" system. "hDOS" provides biomarkers including local, microvascular tissue/blood oxygen saturation (StO₂, in %) and tissue perfusion via the microvascular blood flow index (BFI, in cm²/s). The optical probe was positioned on the *brachioradialis* muscle. In healthy subjects, CO was estimated with a non-invasive hemodynamic monitor (Finapres Medical Systems, Enschede, the Netherlands) while in ICU patients, CO was measured using an invasive hemodynamic monitor (ProAQT, Getinge, Sweden) connected to the patient's arterial line. For both groups, the PLR maneuver was preceded by a 3-minute baseline period with the subject in a semi-recumbent position, followed by 5 minutes of PLR with the legs elevated at 45 degrees, and then a 5-minute recovery phase in which the subject was returned to the semi-recumbent position. All the signals were synchronized in post processing. Both ICU patients and healthy subjects were considered as "responders" if their CO increased by more than 10% relative to baseline during the 30-second period beginning 60 s after the initiation of the PLR maneuver (Δt_{PLR}) [3], as shown in Figure 1. We have computed the changes relative to the baseline as $\Delta r_x(t) = [x(t) - \langle x \rangle_{bsl}] / \langle x \rangle_{bsl}$ % where x is CO and BFI and $\langle \rangle$ is the temporal average over 60 s of stable baseline. For StO₂ the change with

respect to the baseline was calculated as $\Delta x(t) = x(t) - \langle x \rangle_{\text{bsl}}$ %. Within each group, during the Δt_{PLR} changes in StO_2 and BFI (namely $\Delta \text{rBFI}_{\text{PLR}}$ and $\Delta \text{StO}_{2,\text{PLR}}$), reported as mean \pm standard deviation, were compared to the baseline by a paired Wilcoxon signed-rank test. The differences between responders and non-responders, as well as the differences between healthy subjects and ICU patients, were tested with Mann-Whitney U test. All tests significance level was set at $p < 0.05$. A receiver operating characteristic (ROC) curve analysis was utilized to evaluate the performance of a logistic regression model that utilize as input $\Delta \text{rBFI}_{\text{PLR}}$ and/or $\Delta \text{StO}_{2,\text{PLR}}$, or combined.

Results

Among the healthy subjects ($n=23$), 13 (56%) were responders, compared to 4 (31%) among the ICU patients ($n=13$). Figure 1 shows the average changes observed during the PLR maneuver for ΔrBFI (panel a) and for ΔStO_2 (panel b) in the two groups of healthy and ICU patients further divided into responders (red) and non-responders (blue). Bold lines represent the average response, while shaded area the standard deviation across the subjects. Yellow area represents the full duration of the PLR maneuver, while the Δt_{PLR} utilized for calculations is indicated within solid lines. In healthy non-responders ($n=10$), the PLR maneuver induced a change with respect to baseline in $\Delta \text{rBFI}_{\text{PLR}} = 12\% \pm 22\%$, $\Delta \text{StO}_{2,\text{PLR}} = 0.7\% \pm 1.1\%$, and $\Delta \text{rCO}_{\text{PLR}} = 3\% \pm 5\%$, none of which were statistically significant (all $p > 0.25$). In contrast, healthy responders ($n=13$) showed an increase of $\Delta \text{rBFI}_{\text{PLR}} = 21\% \pm 22\%$ ($p = 0.003$), $\Delta \text{StO}_{2,\text{PLR}} = 3\% \pm 1.9\%$ ($p < 0.0001$), and CO increased by 21 ± 14 ($p < 0.0001$). Healthy responders showed a significant increase of $\Delta \text{rCO}_{\text{PLR}}$, and $\Delta \text{StO}_{2,\text{PLR}}$ with respect to healthy non-responders ($p < 0.001$ and $p = 0.006$, respectively).

With respect to baseline, non-responder patients ($n=9$), showed a non-significant increase of $\Delta \text{rCO}_{\text{PLR}} = 2.1 \pm 3.7\%$ ($p = 0.20$), while they showed a statistically significant increase in $\Delta \text{rBFI}_{\text{PLR}} = 11\% \pm 11\%$ ($p = 0.02$) and a significant increase $\Delta \text{StO}_{2,\text{PLR}} = 0.8\% \pm 0.4\%$ ($p = 0.004$). Among responders $\Delta \text{rCO}_{\text{PLR}} = 24\% \pm 15\%$ ($p = 0.125$). Responder patients also exhibited a larger increase in $\Delta \text{rBFI}_{\text{PLR}} = 47\% \pm 31\%$ and an increase in $\Delta \text{StO}_{2,\text{PLR}} = 0.8\% \pm 1.1\%$, though these did not reach statistical significance ($p = 0.125$ and $p = 0.25$, respectively). Finally, responder patients showed a statistically significant larger increase in $\Delta \text{rBFI}_{\text{PLR}}$ with respect to non-responders ($p = 0.005$). Also, $\Delta \text{rCO}_{\text{PLR}}$ was larger in responders ($p = 0.003$).

No notable differences are observed between non-responder healthy and non-responder ICU patients (all $p > 0.05$), while changes in $\Delta \text{StO}_{2,\text{PLR}}$ in responder healthy subjects are notably higher than in ICU patients ($p = 0.03$). No differences in $\Delta \text{rBFI}_{\text{PLR}}$ are reported between responder healthy subjects and responder ICU patients ($p = 0.10$). On the other hand, it is important to note the small sample size of non-responders in the ICU patients ($n=4$).

Finally, in Figure 1 panel c we plot the ROC curves to highlight the predictive performance of $\Delta \text{rBFI}_{\text{PLR}}$, $\Delta \text{StO}_{2,\text{PLR}}$ and their combination for classifying responders and non-responders in both healthy subjects and ICU patients. $\Delta \text{rBFI}_{\text{PLR}}$ alone achieved a sensitivity of 63% and specificity of 82%, with an area under the curve (AUC) of 0.74 ($p = 0.004$). $\Delta \text{StO}_{2,\text{PLR}}$, on the other hand, showed a slightly lower sensitivity of 58% but a higher specificity of 94%, with an AUC of 0.80 ($p = 0.001$). By combining $\Delta \text{rBFI}_{\text{PLR}}$ and $\Delta \text{StO}_{2,\text{PLR}}$ the classification performance improved reaching a sensitivity of 89%, specificity of 82%, and an AUC of 0.87 ($p < 0.001$).

Conclusion and discussion

This study highlights that healthy responders exhibit more pronounced hemodynamic and microvascular oxygenation changes during PLR than ICU patients. However, ICU responders still demonstrate significant changes in $\Delta \text{rBFI}_{\text{PLR}}$, suggesting its potential as a marker of microvascular reactivity, particularly in settings where invasive CO assessment is unavailable.

Current CO monitoring technologies also present challenges in critical care. Their reliability diminishes in patients on vasopressors, particularly with pulse-waveform analysis systems like Pro-AQT. Furthermore, while traditional CO-based fluid management remains standard, hybrid diffuse optics may offer a complementary approach as a surrogate of CO changes by detecting peripheral perfusion and oxygenation changes. This peripheral assessment could help identify false negatives, ultimately aiding in optimizing blood flow. These preliminary findings support further investigation in larger cohorts to confirm the clinical utility of this approach. The study is currently recruiting, and we will present updated results.

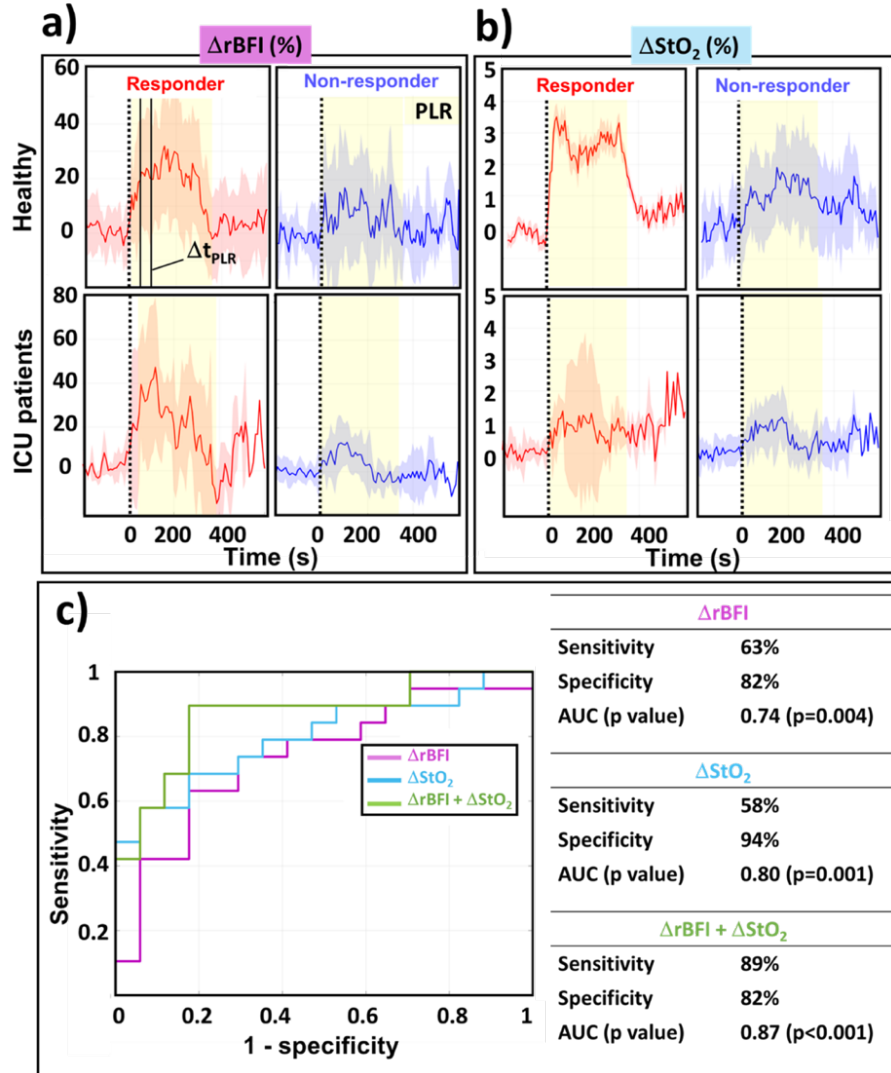


Figure 1 a) time traces for $\Delta rBFI$ and b) for ΔStO_2 where Δ is calculated with respect to a stable 60 s of the baseline period prior to the PLR maneuver. Bold lines correspond to the average values while shaded areas are the standard deviations calculated over all the subjects. The dashed black line indicates the start of the PLR maneuver. The full duration of the PLR is highlighted in yellow. Responders (red) correspond to the subjects whose CO increased more than 10%; non-responders (blue) are subject whose CO remained constant or increased less than 10%. the Δt_{PLR} utilized for calculations is indicated within continuous lines. c) ROC curves for the three logistic regressions where $\Delta rBFI_{PLR}$ and $\Delta StO_{2, PLR}$ are used as independent variables alone (purple and light blue) or combined (green) with the respective sensitivity, specificity and area under the curve (AUC).

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