

Near-Infrared Spectroscopy Reveals Transient Impairment of Microvascular Reactivity During Severe Acute Anaphylaxis

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During severe acute anaphylactic shock, circulating blood volume may decrease by as much as 50%.¹ This has been attributed to an increased vascular permeability with a shift of intravascular fluid into the extravascular space within minutes, resulting in hypotension and hemoconcentration.¹ In the systemic capillary leak syndrome (Clarkson disease),² it has been proposed that the increased vascular permeability is caused by a transient endothelial dysfunction, but in the case of anaphylaxis, evidence for this hypothesis is lacking.

Endothelial function can be assessed by measurement of the postocclusive reactive hyperemia (PORH) response.^{3,4} PORH refers to the reproducible transient increase in blood flow after the release of an arterial occlusion. When the occluding cuff is released, the sudden restoration of blood flow causes an endothelium-dependent, flow-mediated vasodilatation. The velocity and degree of flow restoration depend on the capacity of the microvasculature to recruit arterioles and capillaries, thereby reflecting the integrity of the microcirculation.³

PORH usually is assessed using Doppler flowmetry. Recently, near-infrared spectroscopy (NIRS) has been introduced as a way to quantify the endothelium-mediated changes in vascular tone, elicited by inducing PORH.^{3,4} NIRS has proved to provide excellent reproducibility,^{5,6} and a coherent directional change with simultaneously performed strain gauge plethysmography and radionuclide plethysmography.⁷ In a recent systematic review and meta-analysis, it has been demonstrated that NIRS-derived PORH variables allowed discrimination between normal and abnormal states of microcirculation.⁸

The authors report the PORH response assessed by NIRS in a case of acute anaphylaxis. The responses during this event were suggestive of the presence of transient impairment of microvascular reactivity.

CASE REPORT

A 53-year-old male patient with a history of angina pectoris was scheduled for on-pump coronary artery bypass grafting surgery. There was no history of prior general anesthesia or any allergies. His current medications were rosuvastatine, 5 mg, metoprolol, 50 mg, perindopril, 8 mg, carbasalate cardio, 100 mg, pantoprazol, 40 mg, oxazepam, 4 × 10 mg, and finasteride, 5 mg.

The patient was premedicated with diazepam 10 mg. At arrival in the operating room, standard monitoring was applied, including pulse oximeter, 5-lead electrocardiogram, cerebral oximetry and bispectral index monitor. A 16-gauge catheter was placed in a peripheral vein in the right arm, and an arterial catheter was installed under local anesthesia in the right radial artery.

The patient previously had consented to participate in a prospective, randomized, controlled trial investigating the effect of the priming solution of the cardiopulmonary bypass circuit on microvascular reactivity using NIRS (registered at ClinicalTrials.gov [NCT02034682]). Therefore, 2 disposable NIRS sensors (NIRO-200NX, Hamamatsu Photonics, Tokyo,

Japan) were placed on each forearm in a circumferential orientation (over the brachioradial muscle, about 5 cm distal from the proximal head of the radius). In this study protocol, microvascular reactivity was evaluated by assessment of PORH. A sphygmomanometer cuff (EH50U, Siemens Healthcare, Erlangen, Germany) was wrapped around the arm over the left brachial artery, and arterial occlusion was achieved by inflating the cuff to a pressure of 50 mmHg above the baseline systolic pressure. The cuff was inflated automatically in fewer than 2 seconds to the pressure needed for the arterial occlusion. A standard cuff inflator (Tempco) was used. After 3 minutes of ischemia, the cuff pressure was released rapidly. Tissue oxygen saturation was recorded continuously. Measurements from the contralateral arm were used to control for concurrent non-endothelial-dependent changes in vascular tone (eg, alterations in autonomic tone, transient environmental effects, etc).

Before induction, blood pressure was 143/72 mmHg, and heart rate was 54 beats/min. After adequate preoxygenation, general anesthesia was induced with 350 µg of fentanyl, 30 mg, of propofol, 5 mg of diazepam and 100 mg of rocuronium. Cephazolin 2 g, was administered as antibiotic prophylaxis. The patient was mask ventilated adequately with 100% oxygen. Then a thoracic red flush was noticed, immediately followed by a dramatic fall in arterial blood pressure (62/43 mmHg) and tachycardia (101 beats/min). Marked ST-segment changes were observed on the electrocardiogram. Oxygen saturation decreased from 100% to 93% despite uneventful endotracheal intubation and mechanical ventilation with 100% oxygen in the presence of a normal ventilation with peak pressure of 14 mmHg. Resuscitation was started immediately with 10 µg of epinephrine intravenously along with phenylephrine at a total dose of 2.8 mg, followed by a continuous infusion of norepinephrine at a rate of 0.3 µg/kg/min. At the same time, 800 mL of crystalloids also were administered in order to restore hemodynamic stability. Furthermore, methylprednisolone, 1g, and clemastine, 2 mg, were administered intravenously to treat the anaphylactic reaction. To confirm the diagnosis of anaphylactic shock, a blood sample was obtained to perform a tryptase lab test. Once the patient was hemodynamically stable, it was decided after team discussion to proceed with surgery.

Biochemical findings are presented in Table 1. An arterial blood sample after induction showed a pronounced increase in

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hemoglobin (Hb) from 14.6 g/dL at baseline to 21.7 g/dL after the event. There was also almost a doubling of lactate (9.3 mg/dL to 16.9 mg/dL) and a combined metabolic and respiratory acidosis with a pH that decreased from 7.43 to 7.22. Moderate facial edema was observed.

A prominent capillary leak induced by the anaphylactic reaction was suspected. Therefore, the surgical procedure was converted to an off-pump procedure, and the patient was excluded from the trial. The further course was uneventful, and the patient was transferred to the intensive care unit under minimal vasoconstrictive support with norepinephrine at a rate of 0.15 µg/kg/min. The patient was extubated 7 hours later and discharged from the hospital on the 8th postoperative day. The tryptase lab test was increased significantly (35.2 µg/L; normal value <11.4 µg/L). The patient, however, did not agree to perform further tests to trace the cause of the perioperative anaphylactic shock.

During the surgical procedure, the extent of capillary leak evolution was monitored by sequential PORH measurements. Detailed PORH measurements are presented in Figures 1 to 3. Inflation of the cuff blocked both venous outflow and arterial inflow, producing decreases in oxygenated hemoglobin (oxyHb) (red line) and tissue oxygen saturation (TOI) (green line) and an increase in desoxygenated hemoglobin (desoxyHb) (blue line). OxyHb and desoxyHb are stoichiometric and opposite, such that total blood volume remained unaltered (white line) (the sum of oxyHb and desoxyHb). After release of the occluding cuff, a hyperemic response was observed. Blood volume increased rapidly, causing a rapid increase in oxyHb and a washout of desoxyHb.

Posthoc, numeric parameters were derived from the measured signals in order to quantify the PORH response (Table 2).

PORH Parameters Before the Anaphylactic Event

PORH values before the anaphylactic reaction are presented in Table 2 and displayed in Figure 1. After inflation of the cuff, a progressive decrease of tissue oxygenation was apparent from the oxygen consumption (VO_2) rate and the ischemic response (IR) (calculated as the percent change from baseline to the minimum value).

After releasing the cuff, flow was restored rapidly with the velocity and degree of flow restoration reflecting the adaptation of

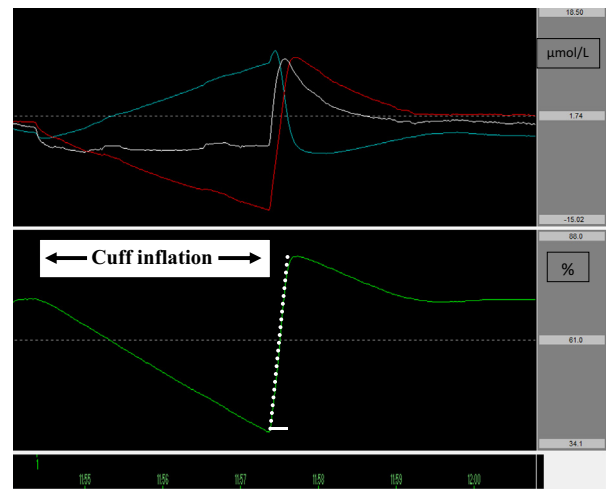


Fig 1. PORH measurements before the anaphylactic event. Inflation of the cuff produced decreases in oxygenated hemoglobin (red line) and tissue oxygen saturation (green line) and an increase in desoxygenated hemoglobin (blue line). Total blood volume remained unaltered (white line). After release of the occluding cuff, blood volume increased rapidly, causing a rapid increase in oxygenated hemoglobin and a washout of desoxygenated hemoglobin. Time axis in minutes. The figure illustrates the short recovery time (solid line, 12 sec) and the fast recovery slope (dotted line, 118%/sec). PORH, postocclusive reactive hyperemia.

the microcirculation. The velocity of flow restoration is assessed by the measurement of t_R (time from release of cuff to initial value), t_M (time from release of cuff to maximum value), and the S_tO_2 recovery slope (recS_tO_2) (calculated by the hyperemic response [HR] divided by t_M). Before the anaphylactic reaction, recovery was very fast, indicated by small recovery times and a fast recovery slope (Table 2). In Figure 1, the fast recovery of flow is illustrated by the solid line for t_R and the dotted line for recS_tO_2 .

The degree of flow restoration is quantified by the hyperemic response (HR), calculated as the percent change from minimum to maximum value. Before the anaphylactic event, HR was 23% and 113% for oxyHb and TOI, respectively. Blood volume change after cuff release was 28%.

Table 1. Biochemical Findings at Different Time Moments

	Before the Anaphylactic Event	After the Anaphylactic Event			
		After Induction of Anesthesia	After Sternotomy	After Heparin	End of Surgery
Hb (g/dL)	14.6	21.7	20.8	20.4	18.2
S_aO_2 (%)	97	97	98	98	99
S_vO_2 (%)	55	81	83	79	81
P_aO_2 (mmHg)	107	115	210	218	265
P_vO_2 (mmHg)	26	53	51	47	53
P_aCO_2 (mmHg)	35	54	48	45	42
pH	7.43	7.22	7.25	7.25	7.31
BE (mmol/L)	-0.6	-6.6	-7.1	-7.8	-5.3
Bic (mmol/L)	23.1	22.1	20.9	19.7	21.0
Lact (mg/dL)	9.3	16.9	14.8	12.1	21.2

Abbreviations: BE, base excess; Bic, bicarbonate; Hb, hemoglobin; Lact, lactate; P_aCO_2 , arterial carbon dioxide partial pressure; P_aO_2 , arterial oxygen partial pressure; P_vO_2 , venous oxygen partial pressure; S_aO_2 , arterial oxygen saturation; S_vO_2 , venous oxygen saturation.

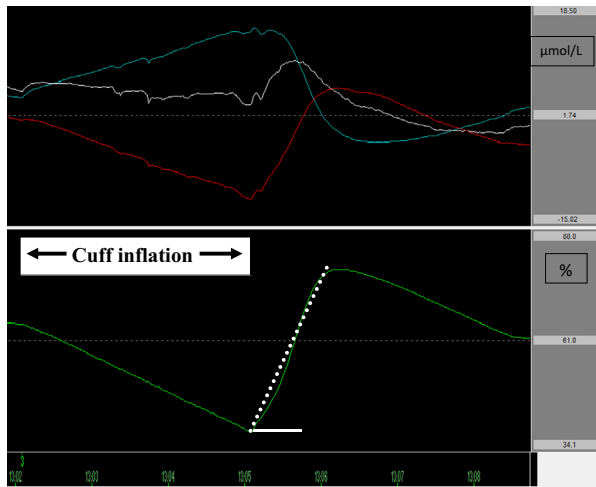


Fig 2. PORH measurements after the anaphylactic event. Inflation of the cuff produced decreases in oxygenated hemoglobin (red line) and tissue oxygen saturation (green line), and an increase in desoxygenated hemoglobin (blue line). Total blood volume remained unaltered (white line). After release of the occluding cuff, blood volume increased rapidly, causing a rapid increase in oxygenated hemoglobin and a washout of desoxygenated hemoglobin. Time axis in minutes. The figure illustrates the significant impairment of microvascular reactivity after the anaphylactic event, indicated by a longer recovery time (solid line, 64 sec), and lower rate of recovery (dotted line, 30%/sec). PORH, postocclusive reactive hyperemia.

PORH Parameters After the Anaphylactic Event

After the anaphylactic event, marked changes in PORH were observed (Table 2; Fig 2). The shape of the signals differed substantially compared to the measurements before the anaphylactic event. VO_2 rate and IR decreased compared to the values before the anaphylactic event, indicating that less oxygen was provided to the tissues during the ischemic phase. After cuff release, the time parameters of recovery (t_R and t_M) were longer, and the rate of recovery (recS_tO_2) as well as the maximal change during recovery (HR and blood volume) were lower compared to the awake parameters. Figure 2 illustrates the significant impairment of microvascular reactivity after the event, indicated by a longer recovery time (time from release of cuff to initial value) (solid line, 64 sec), and lower rate of recovery (dotted line, 30%/sec).

PORH Parameters During Recovery of the Anaphylactic Reaction

At the end of the surgery, PORH parameters partly were restored (Table 2; Fig 3).

DISCUSSION

In the present case, the authors demonstrated a significant impairment of microvascular reactivity after a severe anaphylactic event. PORH measurements demonstrated a decreased oxygen delivery during the ischemic phase and a less pronounced and slower restoration of flow during the reperfusion phase, indicating microvascular dysfunction. PORH parameters partly were restored towards the end of the operation. This

observation indicated the occurrence of a transient impairment of microvascular function during anaphylactic shock.

The precise pathophysiology of shock in anaphylaxis has not yet been characterized fully in humans.⁹ Evidence suggests that the release of numerous immune mediators causes a profound reduction in vascular tone and a major capillary fluid leak, resulting in a mixed distributive-hypovolemic shock.^{9–12} The changes in vascular permeability permit, within minutes, a 50% transfer of the intravascular fluid into the interstitial space causing severe hemoconcentration and hypotension responsible for the anaphylactic shock and a possible lethal outcome.¹ The treatment consists of a combination of measures, including judicious use of intravenous fluids and vasopressors to counter the intravascular volume depletion.^{9,10} However, when the vascular permeability is restored, massive fluid remobilization from tissues into the circulation might result in volume overload and pulmonary edema. Serial PORH measurements might offer the opportunity to monitor the extent and progress of capillary leak and allow for targeting therapeutic strategies accordingly.

In clinical research, the ability of the endothelium to vasodilate in response to physiologic stimuli (PORH response) has been the most widely used clinical endpoint for assessment of endothelial function.^{13,14} Originally, PORH responses were assessed by ultrasound imaging of the brachial artery. However, this technique requires strong expertise and has major technical and interpretive limitations.¹⁵

Recently, the feasibility of NIRS to assess endothelial function has been proposed.^{3–8,16,17} NIRS is a noninvasive technology that continuously measures regional tissue oxygenation. This method is based on the relative transparency of human tissue for near-infrared light and on the existence of

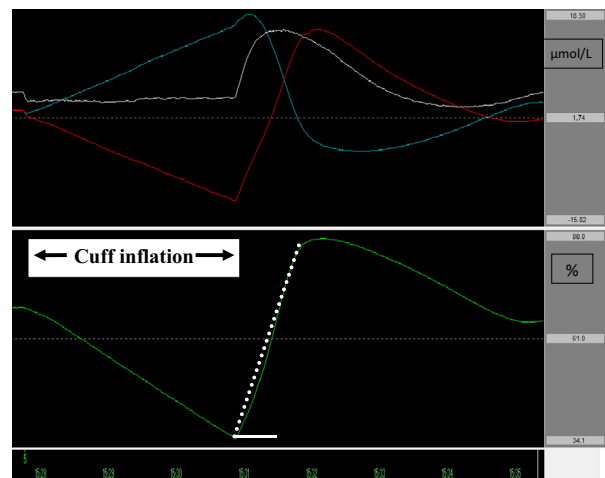


Fig 3. PORH measurements during recovery of the anaphylactic reaction. Inflation of the cuff produced decreases in oxygenated hemoglobin (red line) and tissue oxygen saturation (green line), and an increase in desoxygenated hemoglobin (blue line). Total blood volume remained unaltered (white line). After release of the occluding cuff, blood volume increased rapidly, causing a rapid increase in oxygenated hemoglobin and a washout of desoxygenated hemoglobin. Time axis in minutes. The figure illustrates the partial restoration of microvascular reactivity.

Table 2. Derived NIRS Parameters During PORH at Different Time Points

	Baseline (%)	VO ₂ rate (%/min)	IR (%)	t _R (sec)	t _M (sec)	RecS _t O ₂ (%/sec)	HR (%)
OxyHb							
Before anaphylaxis		5.3	13.3	9	22	63	23
After anaphylaxis:							
Post-induction		3.1	11.5	17	33	33	18
Post-sternotomy		3.4	12.0	39	69	15	17
After heparin		4.7	11.6	62	92	14	21
End of surgery		4.3	13.0	32	71	22	26
DesoxyHb							
Before anaphylaxis		2.6	12.5	17	41	23	16
After anaphylaxis:							
Post-induction		4.2	13.9	34	65	18	19
Post-sternotomy		4.1	10.1	49	97	10	17
After heparin		2.2	12.3	76	119	10	19
End of surgery		4.3	13.5	53	105	11	19
TOI							
Before anaphylaxis	71	15.0	46.0	12	22	118	113
After anaphylaxis:							
Post-induction	66	12.4	39.9	23	40	58	97
Post-sternotomy	65	12.9	40.5	38	64	37	103
After heparin	65	13.1	41.3	64	88	30	116
End of surgery	68	14.7	47.2	39	75	40	138
Blood volume							
Before anaphylaxis							28
After anaphylaxis:							
Post-induction							20
Post-sternotomy							15
After heparin							23
End of surgery							23

Abbreviations: DesoxyHb, desoxygenated hemoglobin; HR, hyperemic response; IR, ischemic response; NIRS, near-infrared spectroscopy; OxyHb, oxygenated hemoglobin; PORH, postocclusive reactive hyperemia; RecS_tO₂, tissue oxygen saturation recovery slope; t_M, time from release of cuff to maximum value; TOI, tissue oxygenation index; t_R, time from release of cuff to initial value; VO₂ rate, oxygen consumption rate.

chromophores in the biologic tissues whose light-absorbing properties vary with oxygenation.¹⁸ Although NIRS has been introduced as a way to quantify endothelium-mediated changes in vascular tone, it has to be emphasized that NIRS does not directly measure microcirculatory blood flow. It is the dynamic change in NIRS parameters in response to a period of ischemic stress (PORH) that provides a means to assess the integrity and functionality of the vascular endothelium.¹⁶ The downslope reflects the oxygen consumption rate, which depends on both the local metabolic demand and the capability of the microcirculation to provide oxygen to the tissue. The recovery slope and the hyperemic response reflect the capability of the microcirculation to adapt to an ischemic challenge by recruitment of the microvascular network.

Several NIRS devices are commercially available. In the present study, the NIRO-200NX was used. NIRO employs the technique of spatially resolved spectroscopy (multiple closely-spaced detectors to measure light attenuation as a function of source-detector separation) to measure TOI and change in hemoglobin. Independently of the spatially resolved spectroscopy method, NIRO measures changes in concentration of oxyHb, desoxyHb, and total hemoglobin, using the modified Beer-Lambert method. Several indices can be used to evaluate microvascular reactivity during the PORH test. Kragelj and his group proposed that the most useful parameters to distinguish

between healthy and impaired peripheral vasculature were the time parameters (t_R and t_M), the rate of reactive hyperemia, and the maximal change of reactive hyperemia.^{6,19} Kragelj also stated that the parameters obtained from the oxyHb signal are the most reliable.^{6,19}

It has been suggested that general anesthesia itself might impair microcirculation. In uncomplicated patients, this impairment manifests as an increased ischemic slope (suggesting a decrease in metabolic rate), a decreased reperfusion slope (suggesting impairment of microcirculatory flow) and an improvement in hyperemic response (indicating the ability to improve local capillary recruitment).²⁰ These results are consistent with what is known about the physiologic effects of anesthesia. However, in the present case, decreased ischemic slope, reperfusion slope, and hyperemic response were observed. Therefore, these changes cannot be attributed to anesthesia-induced impairment of microcirculation.

In summary, this case report showed that microvascular reactivity was impaired in a case of severe acute anaphylaxis. The impairment partially was reversed at the end of the operation. The PORH measured with NIRS proved to be a useful clinical tool in the evaluation of the microcirculation. Sequential PORH measurements offer the opportunity to monitor the extent and progress of capillary leak during acute anaphylaxis and might therefore help in optimizing management.

REFERENCES

1. Practice Parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology: The diagnosis and management of anaphylaxis — An updated practice parameter. *J Allergy Clin Immunol* 115:S483-S523, 2005
2. Xie Z, Ghosh C, Patel R, et al: Vascular endothelial hyperpermeability induces the clinical symptoms of Clarkson disease (the systemic capillary leak syndrome). *Blood* 119:4321-4332, 2012
3. Gerovasili V, Dimopoulos S, Tzanis G, et al: Utilizing the vascular occlusion technique with NIRS technology. *Int J Ind Ergonom* 40:218-222, 2010
4. Nanas S, Gerovasili V, Renieris P: Non-invasive assessment of the microcirculation in critically ill patients. *Anaesth Intensive Care* 37: 733-739, 2009
5. Lacroix S, Gayda M, Gremeaux V, et al: Reproducibility of near-infrared spectroscopy parameters measured during brachial artery occlusion and reactive hyperemia in healthy men. *J Biomed Opt* 17, 2012
6. Kragelj R, Jarm T, Miklavcic D: Reproducibility of parameters of postocclusive reactive hyperemia measured by near infrared spectroscopy and transcutaneous oximetry. *Ann Biomed Eng* 28:168-173, 2000
7. Harel F, Denault A, Ngo Q, et al: Near-infrared spectroscopy to monitor peripheral blood flow perfusion. *J Clin Monit Comput* 22: 37-43, 2008
8. Neto A, Pereira V, Manetta J, et al: Association between static and dynamic thenar near-infrared spectroscopy and mortality in patients with sepsis: A systematic review and meta-analysis. *J Traum Acute Care Surg* 76:226-233, 2014
9. Brown S: The pathophysiology of shock in anaphylaxis. *Immunol Allergy Clin N Am* 27:165-175, 2007
10. Dewachter P, Mouton-Faivre C, Emala C: Anaphylaxis and anesthesia. Controversies and new insights. *Anesthesiology* 111:1141-1150, 2009
11. Khan B, Kemp S: Pathophysiology of anaphylaxis. *Curr Opin Allergy Clin Immunol* 11:319-325, 2011
12. De Bisschop MB, Bellou A: Anaphylaxis. *Curr Opin Crit Care* 18:308-317, 2012
13. Poredos P, Jezovnik MK: Testing endothelial function and its clinical relevance. *J Atheroscler Thromb* 20:1-8, 2013
14. Deanfield JE, Halcox JP, Rabelink TJ: Endothelial function and dysfunction: Testing and clinical relevance. *Circulation* 115: 1285-1295, 2007
15. Corretti MC, Anderson TJ, Benjamin EJ, et al: International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 39:257-265, 2002
16. Doerschug K, Delsing A, Schmidt G, et al: Impairments in microvascular reactivity are related to organ failure in human sepsis. *Am J Physiol Heart Circ Physiol* 293:H1065-H1071, 2007
17. Creteur J: Muscle StO₂ in critically ill patients. *Curr Opin Crit Care* 14:361-366, 2008
18. Moerman A, Wouters P: Near-infrared spectroscopy (NIRS) monitoring in contemporary anesthesia and critical care. *Acta Anaesth Belg* 61:185-194, 2010
19. Kragelj R, Jarm T, Erjavec T, et al: Parameters of postocclusive reactive hyperemia measured by near infrared spectroscopy in patients with peripheral vascular disease and in healthy volunteers. *Ann Biomed Eng* 29:311-320, 2001
20. Bernet C, Desebbe O, Bordon S, et al: The impact of induction of general anesthesia and a vascular occlusion test on tissue oxygen saturation derived parameters in high-risk surgical patients. *J Clin Monit Comput* 25:237-244, 2011