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Microvascular cerebral blood flow fluctuations in association with apneas and hypopneas in acute ischemic stroke

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Abstract. In a pilot study on acute ischemic stroke (AIS) patients, unexpected periodic fluctuations in microvascular cerebral blood flow (CBF) had been observed. Motivated by the relative lack of information about the impact of the emergence of breathing disorders in association with stroke on cerebral hemodynamics, we hypothesized that these fluctuations are due to apneic and hypopneic events. A total of 28 patients were screened within the first week after stroke with a pulse oximeter. Five (18%) showed fluctuations of arterial blood oxygen saturation ($\geq 3\%$) and were included in the study. Near-infrared diffuse correlation spectroscopy (DCS) was utilized bilaterally to measure the frontal lobe CBF alongside respiratory polygraphy. Biphasic CBF fluctuations were observed with a bilateral increase of $27.1\% \pm 17.7\%$ and $29.0\% \pm 17.4\%$ for the ipsilesional and contralesional hemispheres, respectively, and a decrease of $-19.3\% \pm 9.1\%$ and $-21.0\% \pm 8.9\%$ for the ipsilesional and contralesional hemispheres, respectively. The polygraph revealed that, in general, the fluctuations were associated with apneic and hypopneic events. This study motivates us to investigate whether the impact of altered respiratory patterns on cerebral hemodynamics can be detrimental in AIS patients. © The Authors. Published by SPIE under a Creative Commons Attribution 4.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI. [DOI: 10.1117/1.NPh.6.2.025004]

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1 Introduction

Most interventions during the early hours after ischemic stroke onset aim to maximize and stabilize cerebral blood perfusion to diminish the neurological damage and improve the long-term outcome.¹ Furthermore, these patients could be at risk of possible detrimental cerebral blood flow (CBF) fluctuations in the case, for instance, of undiagnosed breathing disorders (BDs). Disordered breathing includes a range of respiratory disorders,² often during sleep, characterized by repetitive reduction (hypopneas) or cessation (apneas) of airflow.

Different types of BDs with different physiological origins have been reported in association with stroke in 10% to 70% of the patients.^{3–12} However, it is not yet clear if the presence of a BD is associated with the long-term outcome. Although some works support the idea that BDs are associated with poor recovery from stroke,^{10,13–16} one study has reported that BDs in stroke patients are associated with early neurological worsening but not with long-term outcome at 6 months.⁴ The reason for the divergence of the results of these studies could be not only the physiological origin of BDs (upper airway obstruction, heart failure, disease, or injury involving the

brain)¹⁷ but also the possible, variable amount of detrimental impact of these events on the cerebral hemodynamics. Thus, the diagnosis, the quantification of these respiratory events, and the characterization of their effect on the cerebral hemodynamics may be relevant for the management of the ischemic stroke patients.

The dynamics of local, microvascular CBF are particularly interesting as, hypothetically, they could reveal that large, repeated changes in the cerebral perfusion could be detrimental when cerebral autoregulation is damaged in the acute stages of stroke.¹⁸ This is relevant during these acute stages as ischemia in the brain is a potentially reversible process dependent on the restoration of the microvascular CBF in the penumbra within a time window of cellular viability that varies on duration and severity of CBF cessation.¹⁹ However, if cerebral autoregulation is damaged, CBF can abruptly increase or decrease without following the needs of the brain and without restoring the needed CBF in the penumbra. If so, BD treatment could be used to avoid these unwanted changes. However, there are no established methods to monitor microvascular CBF at the bedside.

In non-stroke subjects, cerebral hemodynamic fluctuations due to apneas or hypopneas have been extensively studied and characterized previously by several groups by measuring the cerebral blood flow velocity (CBFV) in the middle cerebral artery by transcranial Doppler ultrasound (TCD).^{20–24} However,

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macrovascular CBFV is only an indirect measurement of what happens in the distal microcirculation.

Fluctuations of cerebral hemodynamics have previously been observed in acute stroke patients. A study of nine patients with acute stroke²⁵ reported arterial desaturations from unknown origin that correlated with cerebral hemodynamics measured with near-infrared diffuse optical spectroscopy (NIRS-DOS), and showed an asymmetry of the changes in the two cerebral hemispheres. Pizza et al.²⁶ observed in seven patients with acute/sub-acute middle cerebral artery stroke that obstructive and central apneas were linked to cerebral oxygenation changes by NIRS-DOS. Asymmetrical patterns of cerebral hemodynamic changes were again found with significantly larger changes on the unaffected hemisphere compared to the affected one. However, neither NIRS-DOS nor TCD provide a direct measure of microvascular CBF.

In this pilot study, we have utilized diffuse correlation spectroscopy (DCS), which uses the speckle statistics of near-infrared diffuse light to noninvasively monitor local, microvascular CBF.^{27–29} DCS does not need any exogenous tracers and has been validated against different modalities.^{29,30} In previous studies,³¹ we have observed unexpected fluctuations of microvascular CBF, heart rate (HR), arterial oxygen saturation (SpO₂), and end-tidal carbon dioxide in three (18%) of the seventeen acute ischemic stroke (AIS) patients during the first week from stroke onset, which has motivated the design of this study to investigate the origin of these fluctuations. Here, we have aimed to test the hypothesis that these cerebral and systemic fluctuations were associated with apneic and hypopneic events after stroke.

2 Methods

This study was conducted at the Stroke Unit of Hospital de la Santa Creu i Sant Pau, in Barcelona, Spain, from August 2016 to March 2017. The study protocol was approved by the local ethical committee (EC/15/130). Either the patients or their relatives gave their informed written consent.

The inclusion criteria were being older than 18 years, confirmed ischemic stroke in the anterior circulation, measurement time ≤ 7 days from the stroke onset and written informed consent. The exclusion criteria were resting HR < 40 or > 110 beats per minute (bpm), SpO₂ $< 92\%$, use of oxygen therapy, symptomatic lacunar stroke, previous diagnosis of BDs, previous transient ischemic attack, minor stroke, or intracranial hemorrhage.

The study included two different parts (see Fig. 1, for a flow chart of the procedure). First, patients who fit the clinical inclusion criteria were screened with a pulse oximeter for a minimum

of 4 h between 8 am and 2 pm. Afterward, if the pulse oximeter showed periodic decreases of $\geq 3\%$ in SpO₂, the patients were measured in the afternoon with DCS and also with a respiratory polygraphy device simultaneously for 1 h in the most comfortable head-of-bed position for the patients.

2.1 Neurological Evaluation

Baseline examinations included the collection of a summary of the medical history from patient records (demographics and vascular risk factors) and a clinical examination. The stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS)³² on admission and right after the measurement. Indirect ischemic signs were evaluated by the Alberta Stroke Program Early Computed Tomography Score (ASPECTS).³³ Long-term outcome was evaluated at 3 months by means of the modified Rankin Scale (mRS)³⁴ where a score of > 2 was considered indicative of an unfavorable outcome.

The extent and location of the ischemic area along with the site of arterial occlusion were evaluated on admission by a cranial computed tomography scan and vascular imaging either by angio-computed tomography or by TCD. If patients were eligible, reperfusion therapy (thrombolysis or thrombectomy) was applied.³⁵ Recanalization (either by spontaneous or by revascularization treatment) was assessed with TCD within 24 to 48 h.

The neurological scales were scored by a neurologist or a senior neurology resident blinded to the optical information.

2.2 Optical Methods and Instrumentation

We have used a custom-built DCS,²⁷ which was previously described in other protocols within the same collaboration.^{36–39} Two optical probes were placed on the forehead bilaterally on both hemispheres as lateral as possible, avoiding the sinuses. These probes consisted of a bundle of four detector fiber set at 2.5 cm from a source fiber. We have measured the blood flow index (BFI) continuously with a 2.5-s temporal resolution. The relative CBF changes were obtained by normalizing the calculated continuous BFI with the mean BFI of the first 5 min (baseline) of the measurement. Also, the CBF changes per event were calculated, as explained in Sec. 2.3.

2.2.1 Pulse oximetry and respiratory polygraphy

A standard pulse oximeter (CMS-50D Plus, CONTEC Medical Systems CO, Qinhuangdao, China) was used for the screening of the stroke patients. If these patients were eligible, then they

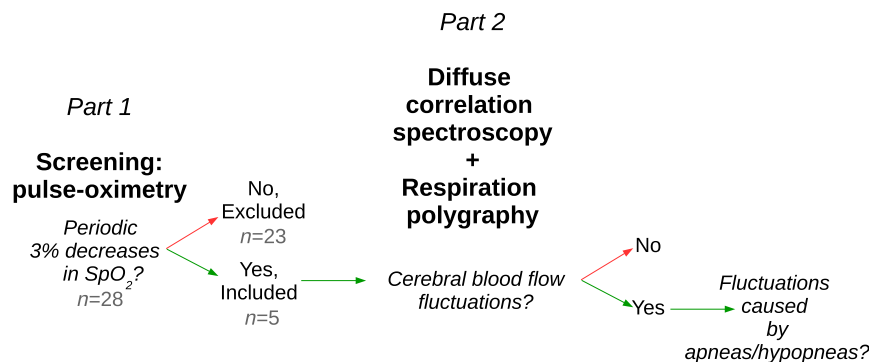


Fig. 1 Methodology of the two parts of the study. The subjects included in each part are depicted in gray. SpO₂, arterial oxygen saturation.

were enrolled for the full study which, in addition to DCS, included a respiratory polygraphy monitoring (Embletta MPR PG, Natus Medical, Middleton, Wisconsin).

The respiratory polygraphy included the recording of the oronasal flow (by a thermistor and a nasal cannula), the thoracic and the abdominal movements (by a respiratory inductance plethysmography band), the SpO₂ and the HR (both by pulse oximetry), among others. The respiratory polygraphy data were further postprocessed by a pulmonologist to determine the following variables: the start and end time points of each event, the event type (obstructive apnea, hypopnea, mixed apnea, or central apnea), the 3% oxygen desaturation index (ODI3), and the number of apneic and hypopneic events per hour of study (AHI).⁴⁰

2.3 Statistical Analysis

To calculate the percentage of CBF change ($\Delta rCBF$) due to each apneic or hypopneic event, we have estimated a basal BFI (BFI_{bl}) as the average of the cerebral BFI from 30 s before the apnea/hypopnea start up to 30 s after the event end. This was considered to correct for slight changes in the probe position during the measurement. Afterward, the CBF changes were calculated as $\Delta rCBF = \left(\frac{BFI}{BFI_{bl}} - 1\right) \times 100$. Similarly, ΔHR was defined as $\Delta HR = HR - HR_{bl}$ and ΔSpO_2 was defined as $\Delta SpO_2 = SpO_2 - SpO_{2bl}$. In all cases, the subscript_{bl} indicates an average over the same period.

Afterward, the events were parametrized for the characterization of the induced $\Delta rCBF$, ΔHR , or ΔSpO_2 for each event. The goal was to study if individual apneic or hypopneic events were associated with significant increases or decreases in these variables as it was hypothesized. This step consisted in considering each event as a function dependent on time [$\Delta rCBF(t)$, $\Delta HR(t)$, and $\Delta SpO_2(t)$], and then, the extrema of these functions along a specific time interval were calculated. The reference time (time zero) was considered as the end of each event. The time windows to find these extrema were considered from -5 to 15 s for the first extremum on $\Delta rCBF$ (see Fig. 2, as an example), from 0 to 15 s for the ΔHR , and from 5 to 35 s for the ΔSpO_2 . These time windows were chosen by visual observation of all the apneas and hypopneas plotted together from -30 to 60 s and according to the literature.^{20,41} These analysis methods have previously been verified in nocturnal measurements of chronic obstructive sleep apnea patients.⁴²

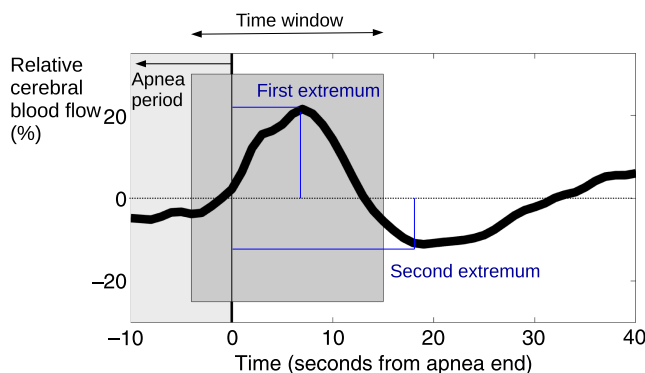


Fig. 2 Cerebral blood flow characterization of individual sleep events, where the apnea end is considered as a pivot point. The light gray region indicates the sleep event. The dark gray region indicates the time window used for finding the first extremum value. The first and second extrema are labeled in blue.

Averages and standard deviations have been performed considering all apneic and hypopneic events for each patient and also for the population. The Wilcoxon signed-rank test was used to assess the difference between ipsilesional and contralesional $\Delta rCBF$ responses. The same test was used to assess if the apneic/hypopneic response of different variables was significantly different from zero. All analyses were performed with MATLAB (Mathworks, Natick, Massachusetts). A p -value < 0.05 was considered to be statistically significant.

3 Results

During the 8-month period, we have screened 28 ischemic stroke patients with pulse oximetry, of whom 5 ($n = 5$, 18%) presented fluctuations ($\geq 3\%$) in SpO₂ and were then included in the second part of the study. Table 1 shows the clinical characteristics of these five patients. Four were male, had an age of 81 ± 6 years (mean \pm standard deviation), an admission NIHSS of 8 (2, 16) [median (first quartile, third quartile)], and a time from stroke onset to measurement of 4 (3, 5) days.

Table 2 shows the results of the DCS and the respiratory polygraphy measurements. In all five patients, the respiratory polygraphy confirmed the presence of altered breathing patterns; two presented periodic breathing [cases 1 and 3; clusters of breaths separated by intervals of apnea (no breathing) or hypopnea], two presented a predominance of obstructive and hypopneic events (cases 2 and 4; the airflow ceased or partially ceased due to upper airway obstruction), and one presented central apneas (case 5; the airflow ceased or partially ceased due to diminished or absent effort to breathe).

Figure 3 shows a representative trace (from case 4) of 10 min of continuous oronasal flow, abdominal and thoracic movements, HR, SpO₂, and CBF changes. This specific interval shows two types of events with good signal-to-noise ratio in the optical data and a “close-up” revealing details. Both apneic (four obstructive apneas, green shading) and hypopneic (three, yellow shading) events are visible and the simultaneous monitoring shows time correlated variation of microvascular CBF, HR, and respiratory variables. From the polygraphy recording, oronasal flow appears to be reduced during the hypopneas and ceases during the obstructive apneas, whereas abdominal and thoracic movements are reduced during these events. HR does not follow a general pattern for this trace. SpO₂ shows a drop with a delay relative to the apneic/hypopneic event. In this time period with frequent events, as commonly observed, the SpO₂ drop of the previous event is overlapped with the next event. It can also be observed that the CBF reaches its maximum at the end of an event. Finally, for this specific interval, periodic breathing is diagnosed but the rest of the acquisition is dominated by obstructive apneic events, as shown in Table 2.

On the contrary, Fig. 4 shows 10 min of similar traces where neither fluctuations nor apnea/hypopnea events are found. This patient (case 3) is the only one with no apneic/hypopneic events during those 10 min.

For completeness, the full data set for the five patients can be found in Sec. 5 Appendix.

From the five patients, 239 ($n = 239$) apneic/hypopneic events were analyzed. In all patients, the CBF changes were biphasic. In other words, significant bilateral CBF increases of $27.1\% \pm 17.7\%$ ($p < 0.001$) for the ipsilesional and $29.0\% \pm 17.4\%$ ($p < 0.001$) for the contralesional hemispheres were followed by decreases of $-19.3\% \pm 9.1\%$ ($p < 0.001$) for the ipsilesional and $-21.0\% \pm 8.9\%$ ($p < 0.001$) for the contralesional

Table 1 Demographics and prestroke clinical characteristics (top) and poststroke clinical characteristics (bottom) of the five ischemic stroke patients.

Case	1	2	3	4	5
Age (y), gender (M/F)	83, F	73, M	82, M	89, M	76, M
Smoking	Former	Former	Former	Former	Former
Arterial hypertension	Yes	Yes	No	No	No
Dyslipidemia	Yes	Yes	No	No	No
Diabetes	No	No	Yes	No	Yes
Ipsilesional ICA stenosis >70%	Yes	No	No	—	No
Coronary disease	No	No	Yes	No	Yes
Atrial fibrillation	No	No	No	No	No
Left ventricular ejection fraction (%)	>50	40 to 50	40	—	25
Arterial occlusion	Left MCA	Left MCA	Right ACA	Left MCA	Right MCA
NIHSS admission	7	7	3	20	21
NIHSS after the measurement	2	1	8	16	21
Reperfusion therapy	Yes	Yes	No	No	No
Recanalization	Yes	No	Yes	No	No
Infarct location	Insular and frontal	Insular and frontal	Frontal	Insular, temporal, and basal ganglia	Insular, temporal, and parietal
ASPECTS	8	8	10	6	6
Days from stroke to measurement	7	4	3	5	0
mRS 3 months	2	1	4	6	6

Note: M, male; F, female; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; and mRS, modified Rankin Scale.

hemispheres were found due to each apneic/hypopneic event. There was no interhemispheric difference between the maximum increases ($p = 0.189$) or the maximum decreases ($p = 0.053$). However, this result suggested a trend toward a potential difference between hemispheres, as it has been previously found by NIRS-DOS,^{25,26} as mentioned in Sec. 1. Also, as expected, HR increased ($p < 0.001$) by 6.5 ± 6.8 bpm and SpO₂ decreased ($p < 0.001$) by $-4.9\% \pm 16.8\%$.

The two patients (cases 4 and 5) with the highest AHI, one with predominance of an obstructive apnea pattern and the other with predominance of a central apnea pattern, had the two highest NIHSS both on admission and after the measurement and the lowest ASPECTS. Unfortunately, both had a mRS of 6, i.e., they had died during the 3 months after stroke onset. Of these two patients, the one with the highest AHI (case 5) also presented the lowest left ventricular ejection fraction. However, neither of these two patients presented the highest physiological or cerebral hemodynamic changes in response to the respiratory events. One of the characteristics of the remaining three patients (cases 1, 2, and 3) with lower stroke severity was that they presented mainly hypopneic events, in comparison to the

obstructive and central apneas found in the two most severe patients (cases 4 and 5). We note that, given the small population, these were just anecdotal statements and should not be considered generalizable.

4 Discussion

In this study, we have followed up on our previous observation of unexpected bilateral fluctuations in microvascular CBF in patients with anterior, cerebral ischemic stroke that were observed in different protocols with DCS measurements.³¹ We have hypothesized that these fluctuations were due to BDs, in particular, due to apneic and hypopneic events. Therefore, a protocol based on prescreening for these events with a pulse oximeter was introduced to enroll patients without a previous diagnosis of BDs for follow-up study combining respiratory polygraphy and DCS. A careful evaluation was carried out to identify the origin of these fluctuations and to characterize their details by combining this recording of different respiratory variables, SpO₂, and HR. Apneic and hypopneic events were determined to be associated with the effect of cerebral hemodynamics and this effect was characterized.

Table 2 Polygraphic characteristics (top) and maximum CBF, HR and SpO₂ changes due to each apneic/hypopneic event (bottom) of each patient.

Case	1	2	3	4	5
AHI (n/hour)	45.6	13	24.8	45.8	63.8
ODI3 (%)	46.3	15.7	17.4	48.1	10
Obstructive apneas, <i>n</i>	0	0	1	31	1
Central apneas, <i>n</i>	1	0	2	0	82
Mixed apneas, <i>n</i>	0	0	1	0	0
Hypopneas, <i>n</i>	37	13	20	30	0
Event duration (s)	21 ± 7	24 ± 4	27 ± 8	30 ± 11	19 ± 5
BD	Periodic respiration	Hypopneas	Periodic respiration	Obstructive events	Central apneas
Max. increase-induced ΔrCBF _{ipsi} (%)	30.0 ± 12.7	37.4 ± 13.0	22.4 ± 8.9	31.0 ± 10.1	21.9 ± 23.9
Max. increase-induced ΔrCBF _{contra} (%)	32.9 ± 21.4	27.6 ± 11.0	29.7 ± 15	36.1 ± 11.2	21.7 ± 18.3
Max. decrease-induced ΔrCBF _{ipsi} (%)	-19.2 ± 7.0	-33.3 ± 12.1	-16.1 ± 8.2	-24.2 ± 6.6	-13.6 ± 5.8
Max. decrease-induced ΔrCBF _{contra} (%)	-17.8 ± 7.4	-25.4 ± 11.1	-19.9 ± 8.1	-28.0 ± 8.1	-16.3 ± 5.3
Max. increase-induced ΔHR (bpm)	2.8 ± 1.6	14.8 ± 8.0	16.0 ± 6.8	10.6 ± 4.3	1.1 ± 0.7
Max. decrease-induced ΔSpO ₂ (%)	-2.2 ± 1.0	-1.6 ± 0.7	-1.5 ± 9.3	-9.9 ± 24.6	-0.9 ± 0.8

Note: AHI, apnea-hypopnea index; ODI3, 3% oxygen desaturation index; ΔrCBF, relative cerebral blood flow changes; ΔHR, HR changes; ΔSpO₂, arterial oxygenation saturation changes; Max., maximum; ipsi., ipsilesional hemisphere; contra., contralesional hemisphere; and *n*, number of events detected; mean±standard deviation.

As observed by the full data set in the Sec. 5 Appendix, the precise nature of the cause of the microvascular CBF changes is not absolutely clear from this study, i.e., some CBF fluctuations lead the apnea/hypopnea, whereas others follow it. This may be partially due to errors in the precise synchronization of the measurements but it may also have further implications indicating secondary events that may have caused respiratory effects, such as cortical spreading depression^{43–45} in the brain stem.^{46,47} However, our study did not gather definitive evidence (e.g., recordings at multiple locations to demonstrate any spreading activity and/or recordings of the electrical activity) to accept or refute this possibility. These results have encouraged us to look further and deeper into this issue in future studies by combining multimodal, precisely synchronized diffuse optical recordings with polygraphy, capnography, and electroencephalography, and a larger head coverage with multiple source and detector pairs.

By the polygraphy, HR and SpO₂ changes were found during these events. These HR and SpO₂ changes followed the apneic/hypopneic dynamics expected by the literature in patients with BDs,^{20,24,41,48,49} showing an increase during the event or at the end of it for the HR, and a decrease after the end of the event for the SpO₂. No periodicity in the respiratory changes was found, as shown in the full data set in Sec. 5 Appendix, as the periodicity depended on the pathogenic mechanism, on the sleep stage, and on the position, among others.⁵⁰

In non-stroke patients with BDs, several studies have reported CBFV changes measured by TCD as showing an increase close to the end of the apnea.^{20,23,24} Our findings are similar; we have observed a CBF increase of $27.1\% \pm 17.7\%$

and $29.0\% \pm 17.4\%$ for the ipsilesional and contralesional hemispheres, respectively, and a decrease of $-19.3\% \pm 9.1\%$ and $-21.0\% \pm 8.9\%$ for the ipsilesional and contralesional hemispheres, respectively, close to the end of the apneic/hypopneic events. This increase is similar to the CBF increase of $30\% \pm 17\%$ and the decrease of $-20\% \pm 12\%$ described previously by us using DCS in obstructive sleep apneic events.⁴² It is also consistent with the CBFV of 22% to 42% increase found by Alex et al.²³ and also to the $14.6\% \pm 14\%$ increase right after the apnea end by Bålfors and Franklin.²⁰ However, other authors have found larger CBFV increases.^{21,24}

These results show that there is a decrease in cerebral perfusion due to an apneic or hypopneic event. If these intermittent decreases lead to ischemia, they can cause hypoxic/ischemic brain injury, especially if cerebrovascular reactivity and regulation are impaired, which is often the case in ischemic stroke patients.^{51,52} Consequently, this could lead to a worsened prognosis, which may call for interventions such as continuous positive airway pressure (CPAP) therapy. We note that, to date, no direct link among a degree of microvascular CBF changes, the long-term outcome, and the use of CPAP therapy has been studied.

Several works have studied the general effect of CPAP therapy, mainly in obstructive disorders or adaptive servo-ventilation (ASV) treatment for central disorders to avoid apneas and hypopneas.^{53–55} In stroke patients, whereas some authors support the benefits of the CPAP treatment on BDs,^{15,56–61} others claim that these benefits are not clear^{62,63} or that there is no benefit at all.⁶⁴ Nevertheless, as mentioned earlier, BDs diagnosis and CPAP or ASV treatment are not the common practice in the stroke units.

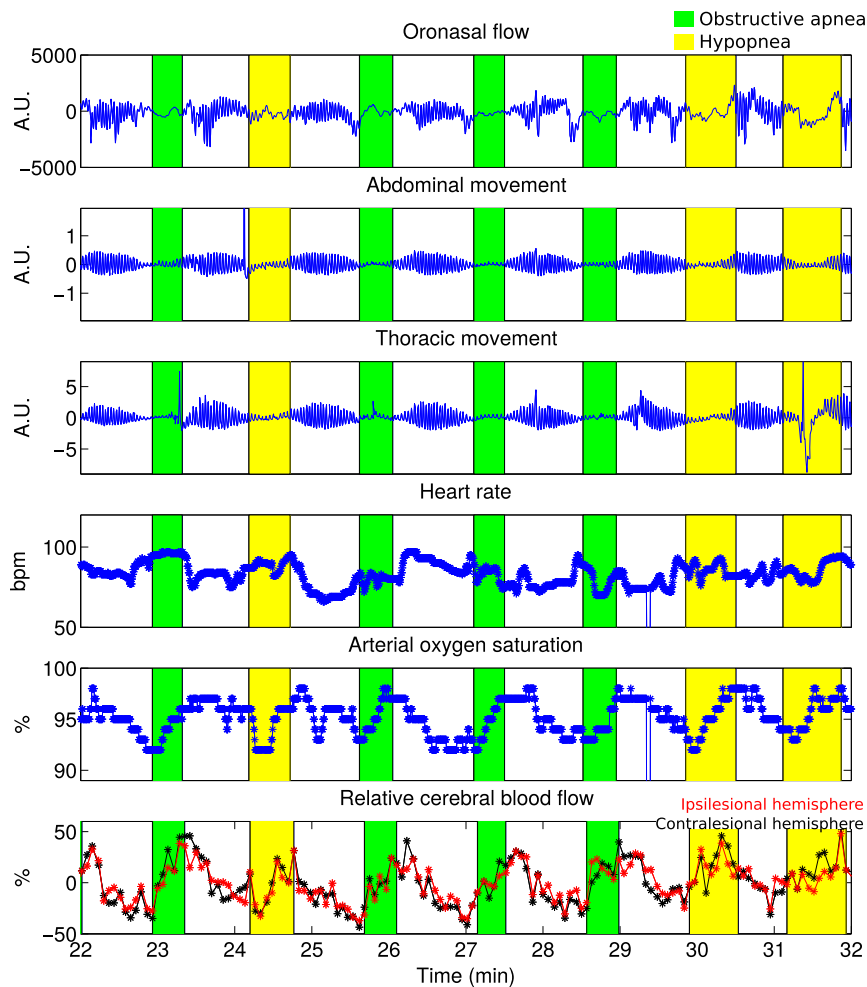


Fig. 3 A 10-min trace of systemic fluctuations of physiological variables alongside the fluctuations of CBF. Red and black CBF traces correspond to the ipsilesional and contralateral hemispheres, respectively. Hypopneas (yellow) and obstructive apneas (green) are shown from the measurements of an 89-year-old male with a left middle cerebral artery ischemic stroke (case 4). The patient presented a left middle cerebral artery stroke with insular, temporal, and basal ganglia ischemic areas. The NIHSS score was 16 when measured. The patient died after 24 h of the measurement.

Future work with a larger sample size to investigate if the CPAP or ASV could be effective in those patients who show the presence and/or large fluctuations in CBF (e.g., above a threshold) in relation to apneic/hypopneic events is warranted. In addition, it would be of interest to study if all ischemic stroke patients with apneic/hypopneic events show similar CBF fluctuations, or if there is an interindividual variability in the response to apneas or hypopneas, and, consequently, the response to treatment may be different.

In our cohort, the two patients (cases 4 and 5) with the highest AHI were those with the worse stroke severity (higher NIHSS score) at the moment of the measurement. This has been previously reported in patients with stroke showing central BDs.¹³ Similarly, the ASPECTS score of these two patients were the lowest of the group, which was compatible with the idea that large acute cerebral hemispheric lesions were associated to BDs.^{7,65} One of these two severe patients (case 5; case 4 had no information available) presented heart failure [low left ventricular ejection fraction (<40%)] and mainly central events, as it has been found in stroke patients in association with central BDs.⁶ The BD present in this patient could be related to it.

Insular and frontal ischemic regions were present in our cohort and, interestingly, these regions have already been associated to BDs of central origin.^{13,65,66} However, other works have supported the idea of the lack of an association between the presence of BDs of central origin and the location of stroke.^{5,9,11} Nevertheless, more patients are needed to clearly identify clinical associations.

Our proof-of-concept study has some limitations, including the small number of patients included in the final analysis, the different types of possible BDs with different physiological origins, and the short recording time of DCS simultaneously with respiratory polygraphy. Future studies will add more subjects and will measure these subjects during several hours continuously in order to better identify the type of BD, and moreover, to link it to the degree of the cerebral hemodynamic responses, among other previously mentioned goals.

Another limitation is that only one measurement per patient has been performed for this study, so we could not track the start and cessation of the fluctuations together with the clinical stroke evolution. Anecdotally, in our previous protocols,^{31,67} the physiological fluctuations observed have

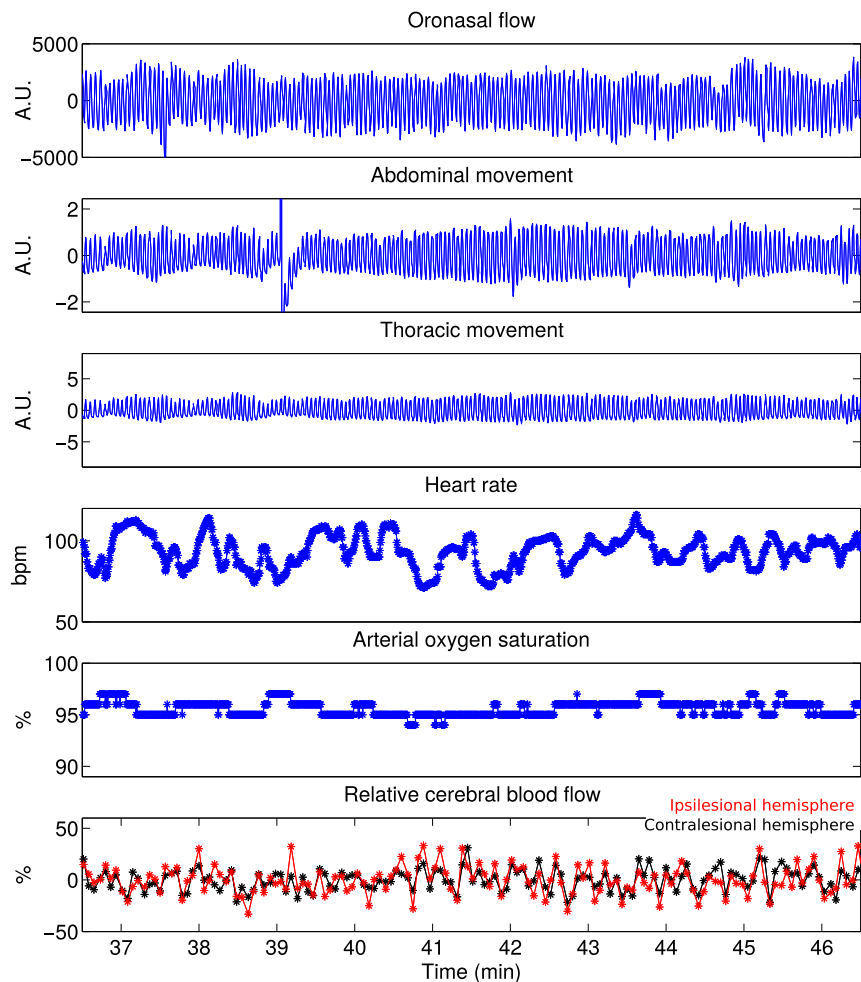


Fig. 4 A 10-min trace with no typical fluctuations of cerebral blood and no apneas or hypopneas. Red and black CBF traces correspond to the ipsilesional and contralesional hemispheres, respectively. Measurements of an 82-year-old male with a right anterior cerebral artery ischemic stroke (case 3) are provided. The patient had a blockage of the right anterior cerebral artery with a frontal ischemic area. The NIHSS score was 8 when measured.

prevailed in the different measurements performed in each patient during the first week after stroke. Accordingly, it is expected that BDs could be present during the first week after stroke in the case of patients with BDs of central origin, as BDs have been found to resolve after several weeks.⁶⁶ Future studies should include daily measurements to track when these fluctuations cease and to relate it to clinical parameters.

Owing to the small number of subjects considered for this analysis, we have avoided a group analysis. Two important parameters to understand CBF changes are the blood pressure and the end-tidal carbon dioxide; future studies should include their simultaneous measurement with DCS. Different studies have suggested these two parameters as different primary drivers to the CBFV changes during apneas. Przybyłowski et al.⁶⁸ suggested that carbon dioxide is the primary regulator, and not the blood pressure, of the rise in CBFV (measured by TCD) during apnea and in the reduction of CBFV in the following apnea. On the contrary, Yaggi and Mohsenin⁶⁹ suggested that if autoregulation is impaired or the changes in blood pressure are sufficiently rapid that an intact autoregulation does not have time to adapt, then the changes in TCD velocity could be related

to the changes in blood pressure. However, these studies only focus on the macrocirculation level; on the microcirculation level, these parameters may have a different influence on microvascular CBF. Moreover, hypoxia has been found during apneic events,^{70,71} which could also contribute to the local microvascular change.

Finally, diffuse optical spectroscopy techniques not only provide information from the brain but also contain scalp and skull contributions.^{29,72} In this work, instead of including a small source–detector separation (1 cm) to study the superficial effects, we have kept all detectors for large separations to focus on improving the signal-to-noise ratio, as a source–detector separation of 2.5 cm has been found to be a good compromise.^{29,30,73} Future implementations could utilize more source–detector pairs as well as a pressure modulation protocol to minimize this effect.⁷⁴

In conclusion, DCS has successfully revealed bilateral fluctuations in CBF of ischemic stroke patients with undiagnosed BDs, in accordance with systemic fluctuations of physiological variables. These cerebral hemodynamic fluctuations are related to apneic and hypopneic events in the five patients tested. Further studies are needed to study the possible detrimental

impact of the magnitude and presence of these cerebral hemodynamic fluctuations, especially in the early hours after stroke where the interventions are more relevant to the outcome, for the recovery of stroke patients.

5 Appendix

The full data set for the five patients measured is shown in Figs. 5–9.

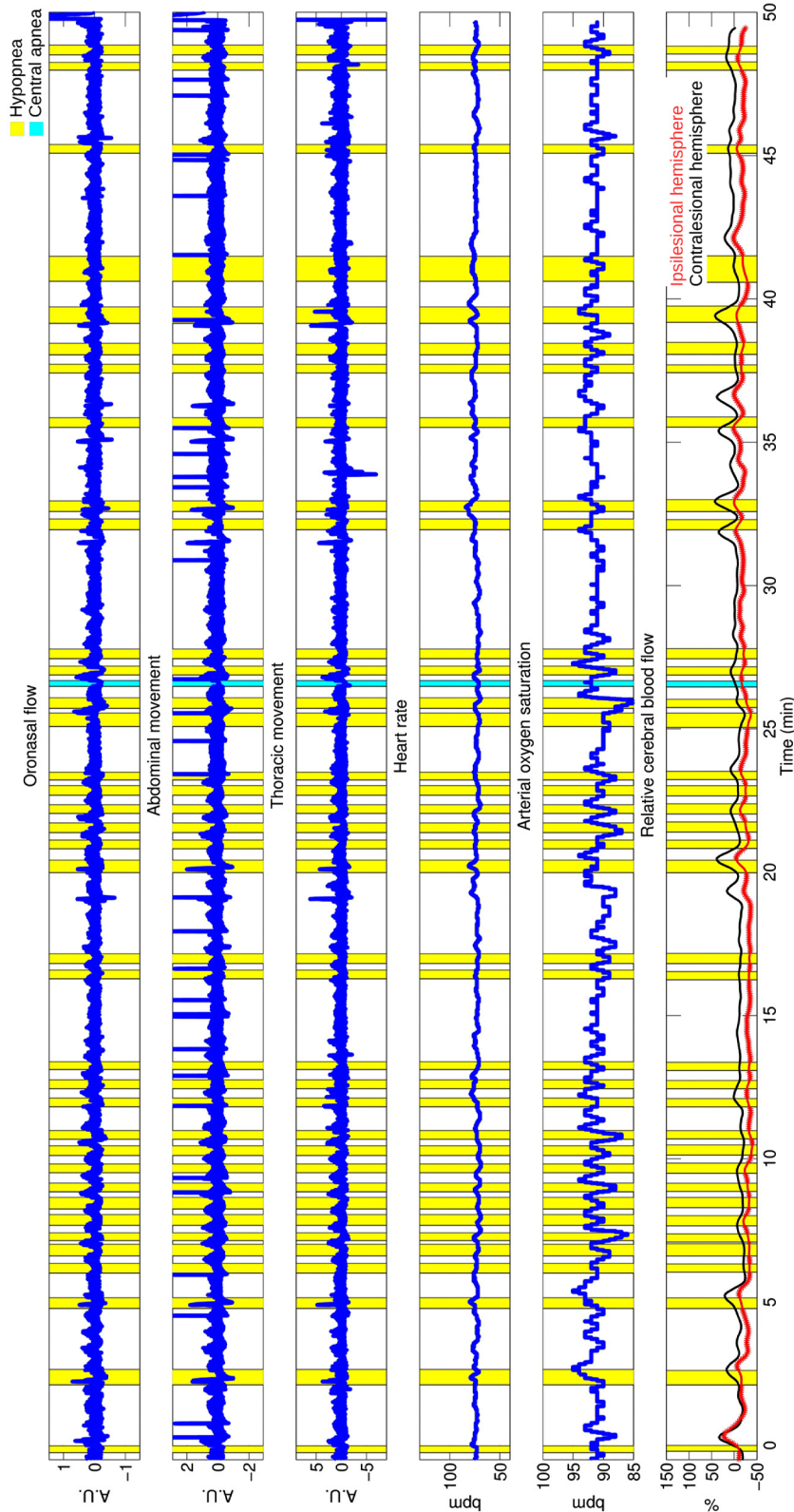


Fig. 5 The full trace recording of case 1 showing periodic respiration, with mainly hypopneic events. Hypopneas are depicted in yellow and central apneas in light blue. Red and black CBF traces correspond to the ipsilesional and contralateral hemispheres, respectively.

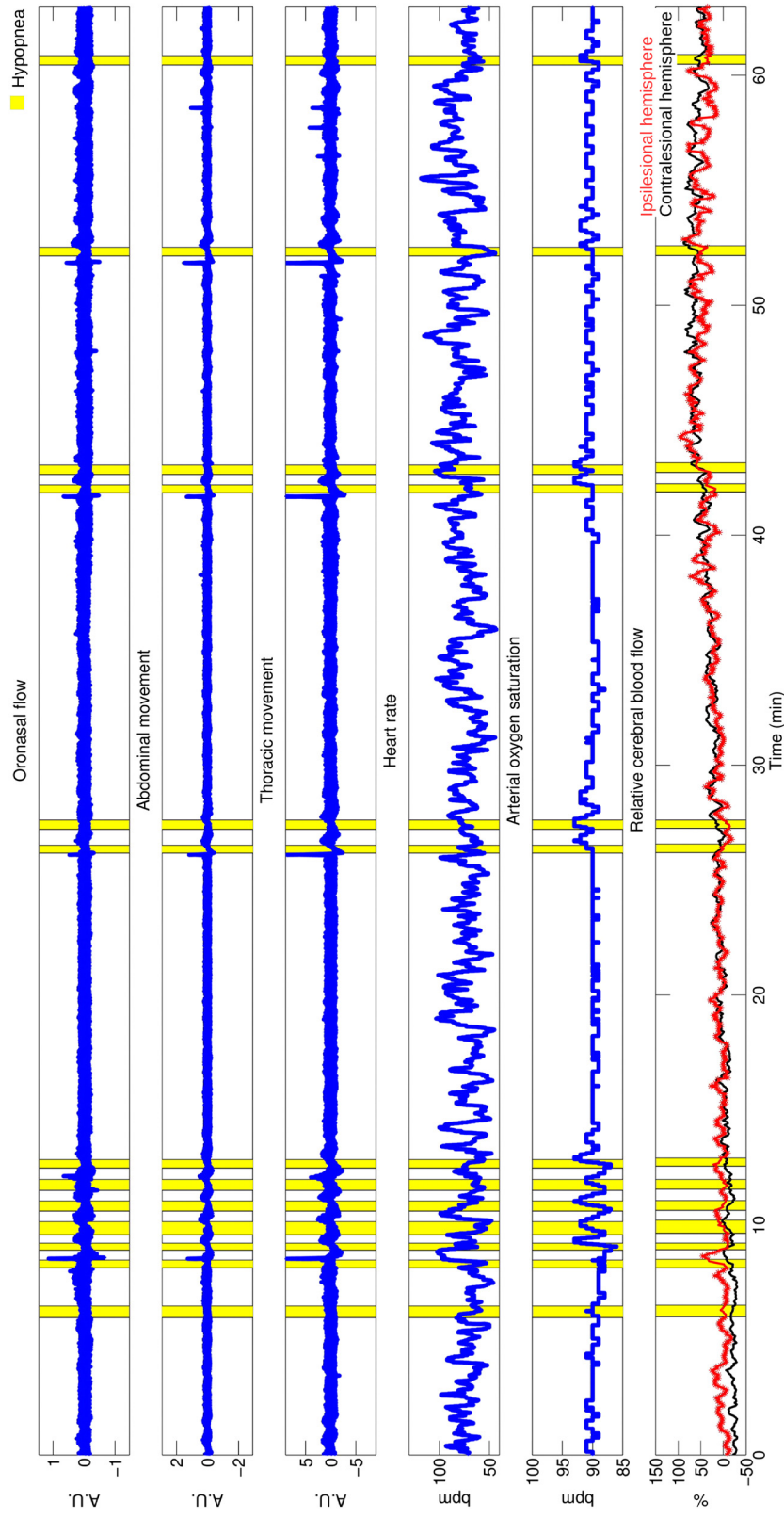


Fig. 6 The full trace recording of case 2 showing only hypopneic events (in yellow). Red and black CBF traces correspond to the ipsilesional and contralateral hemispheres, respectively.

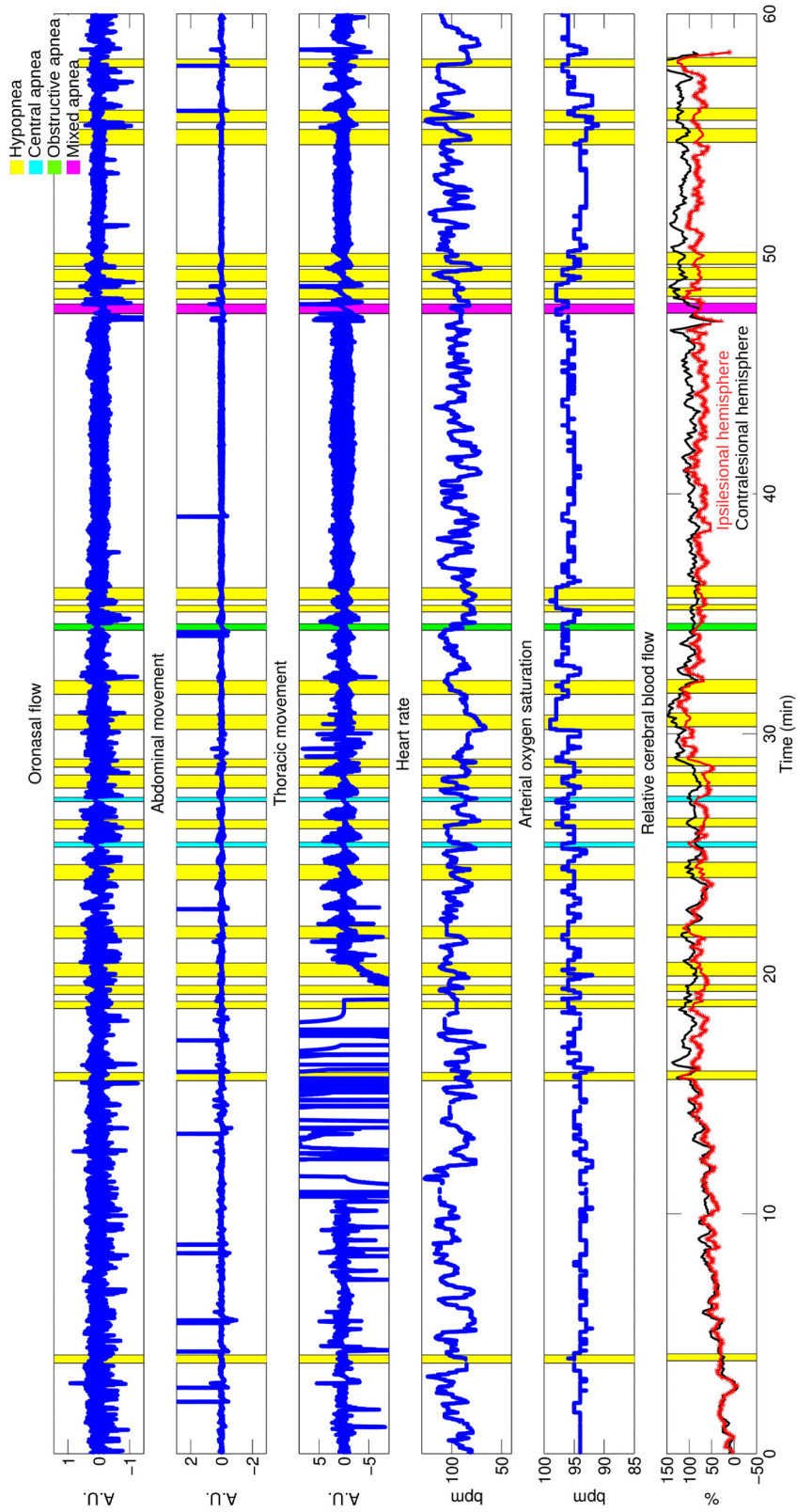


Fig. 7 The full trace recording of case 3 showing periodic respiration, with mainly hypopneic events. Hypopneas are depicted in yellow, central apneas in light blue, obstructive apneas in green, and mixed apneas in magenta. Red and black CBF traces correspond to the ipsilesional and contralateral hemispheres, respectively.

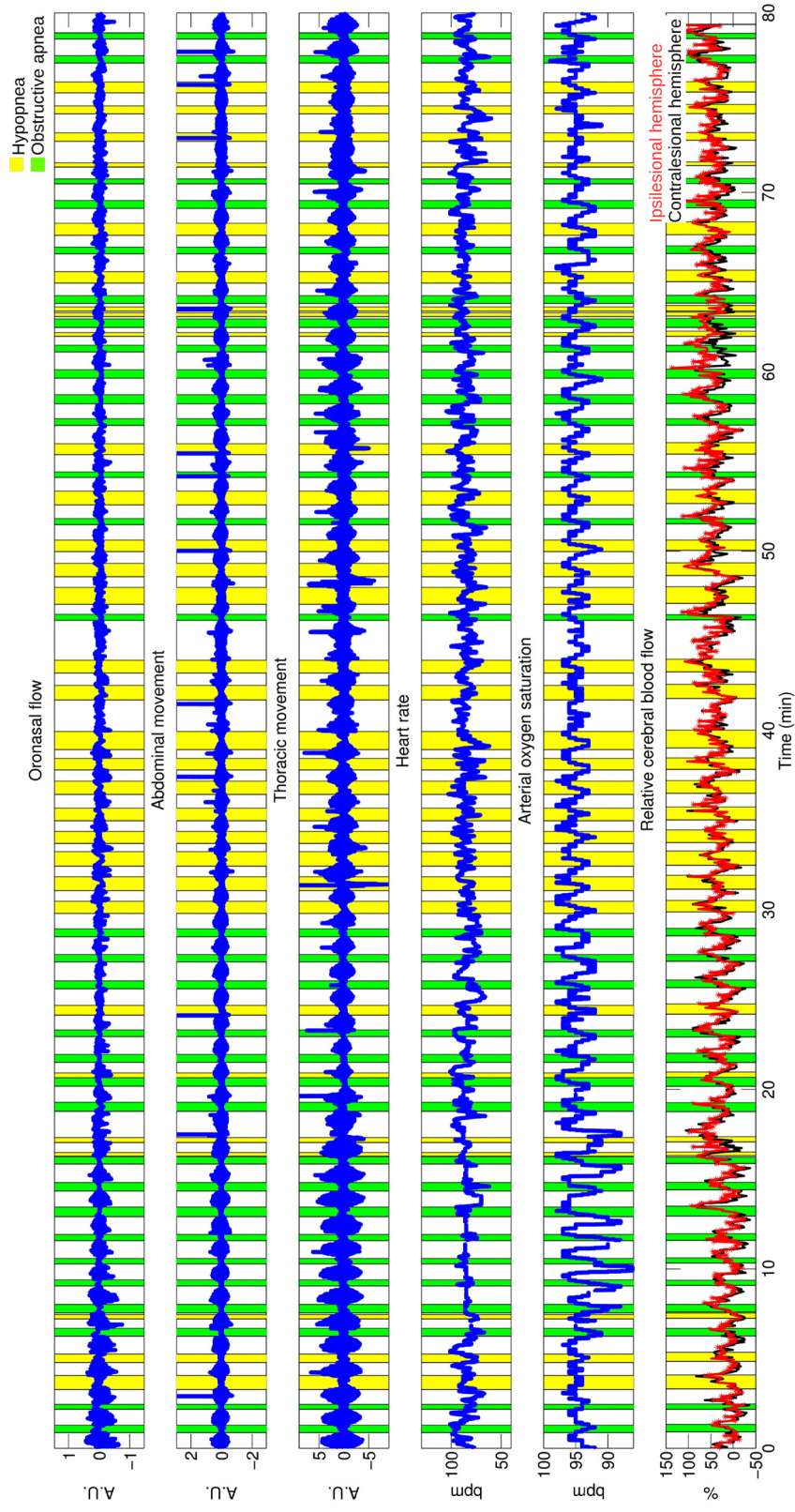


Fig. 8 The full trace recording of case 4 showing both obstructive (in green) and hypopneic (in yellow) events. Red and black CBF traces correspond to the ipsilesional and contralesional hemispheres, respectively.

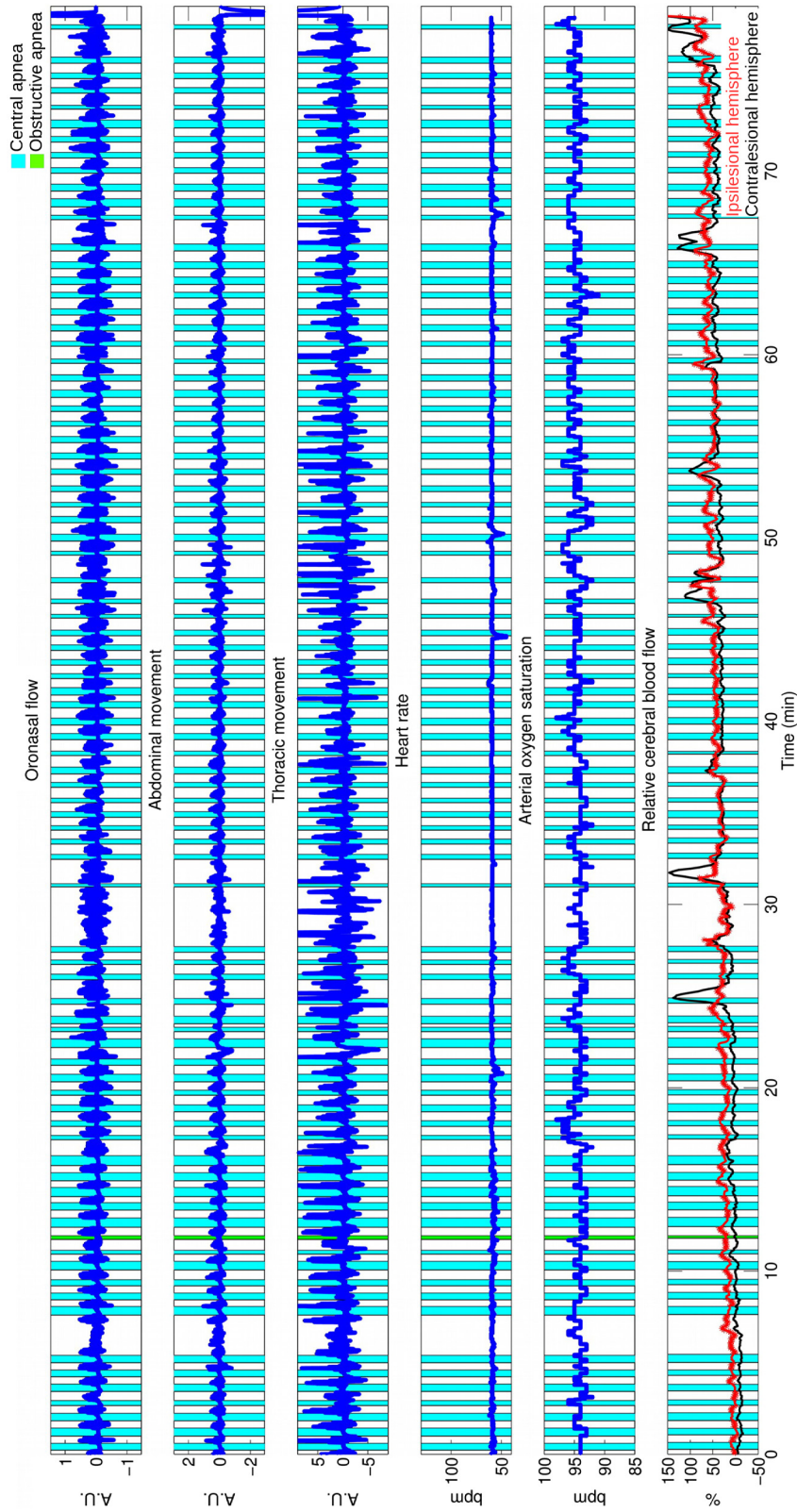


Fig. 9 The full trace recording of case 5 showing central apneic events (in light blue). Obstructive apneas are depicted in green. Red and black CBF traces correspond to the ipsilesional and contralateral hemispheres, respectively.

Disclosures

Herewith the following current or potential financial relationships are disclosed. ICFO has equity ownership in the spin-off company HemoPhotonics S.L. Potential financial conflicts of interest and objectivity of research have been monitored by ICFO Knowledge & Technology Transfer Department. No financial conflicts of interest were identified.

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