MEASURING CHANGES IN CEREBRAL OXYGENATION AND HEMODYNAMICS DURING OBSTRUCTIVE SLEEP APNEA BY FUNCTIONAL NEAR INFRARED SPECTROSCOPY

by

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ABSTRACT

MEASURING CHANGES IN CEREBRAL OXYGENATION AND HEMODYNAMICS DURING OBSTRUCTIVE SLEEP APNEA BY FUNCTIONAL NEAR INFRARED SPECTROSCOPY

One of the most important integral part of human existence is sleep. It has been thought that sleep has a recovery function for brain. This importance opens a new area of research about sleep disorders. Obstructive sleep apnea occurs with the absence of airflow for more than ten seconds despite continuing ventilatory efforts, several times during sleep with a reduction of arterial oxygen saturation (SaO2).

Sleep apnea can clinically be detected by overnight polysomnography studies, but these studies do not give information about brain hemodynamics and tissue oxygenation. Functional imaging of brain by near infrared spectroscopy (fNIRS), gives chance to measure specific biochemical markers. It is also possible to continuously and noninvasively measure cerebral oxygenation by NIRS.

In this study, by using functional near infrared spectroscopy synchronously with polysomnography; cerebral tissue oxygenation and hemodynamics of six obstructive sleep apnea (OSA) patients were measured with the certain polysomnography parameters, like SaO2 and respiratory signal.

During apneic events, cerebral tissue deoxygenation was not as significant as deoxygenation in peripheral tissues. In this study, during apneic events, increase in deoxy-hemoglobin and total hemoglobin were observed in combination with a lesser increase in oxy-hemoglobin in cerebral tissue Phase differences between breathing, arterial oxygen saturation and cerebral tissue hemodynamics were also observed during this study.

Keywords: Sleep, Apnea, Functional near infrared spectroscopy, Brain hemodynamics

ÖZET

İŞLEVSEL YAKIN KIZILÖTESİ SPEKTROSKOPİ YÖNTEMİ İLE OBSTURUKTİF UYKU APNESİ SIRASINDA BEYİN OKSİJENASYONU VE HEMODİNAMİĞİNİN ÖLÇÜLMESİ

İnsanın var oluşunun en önemli bölümlerinden biri uykudur. Uykunun, beyinin kendisini yenilemesi ve iyileştirmesinde büyük önem taşıdığı düşünülmektedir. Bu önemli özellik, uyku bozuklukları ile ilgili yeni bir araştırma alanı ortaya çıkarmıştır. Uyku apnesi sendromu, uyku sırasında nefes alma çabasının devam etmesine rağmen hava akışının on saniyeden daha uzun sürelerde kesilmesi ve bu esnada arteriyel oksijen saturasyonunda düşme meydana gelmesiyle oluşur.

Uyku apnesi, klinik anlamda polisomnografi çalışmaları ile teşhis edilmektedir; fakat bu çalışmalar beyin hemodinamiği ve doku oksijenlenmesi hakkında bilgi vermemektedir. İşlevsel yakın kızıl ötesi spektroskopi (IYKOS) tekniği, belirli bazı kimyasal işaretleyicilerin ölçülmesine olanak tanımaktadır. IYKOS ile, sürekli ve invazif olmayan bir yöntemle beyin oksijenasyonunu takip etmek mümkündür.

Bu çalışmada; IYKOS ile polisomnografi eş zamanlı bir şekilde kullanılarak, obsturuktif uyku apneli altı hastada, beyin dokusu oksijenasyonu ve hemodinamiği ile arteriyel oksijen saturasyonu ve nefes alma parametreleri gibi standart polisomnografi parametreleri ölçülmüştür. Apne sırasında beyin dokusu oksijenlenmesindeki azalmanın, vücudun diğer bölgelerindeki oksijenlenme azalmasına göre çok daha küçük olduğu anlaşılmaktadır. İncelenen apne olayları sırasında deoksi-hemoglobin ve toplam hemoglobinde fark edilir bir artma gözlenirken, oksi-hemoglobinde bu artış daha düşük bir şekilde gerçekleşmiştir. Bu çalışmada ayrıca, apne sırasında nefes alma, arteriyel oksijen saturasyonu ve beyin hemodinamik parametreleri arasındaki faz farkları da incelenmiştir.

Anahtar Sözcükler: Uyku, Apne, İşlevsel yakın kızılötesi spektroskopi, beyin hemodinamiği

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SaO_2	Arterial Oxygen Saturation
HBO_2	Oxy-hemoglobin
HB	Deoxy-hemoglobin
tHB	Total-hemoglobin
SO_2	Cerebral Tissue Oxygen Saturation
kg/m^2	Kilograms per meter square
nm	Nanometer
cm	Centimeter
mm	Millimeter
Hz	Hertz
µmol/L	Micromoles per liter
$\Delta_n SaO_2$	Normalized decrease in SaO_2
$\Delta_n SO_2$	Normalized decrease in SO_2
t_a	Apnea duration
λ	Wavelength
ε	Molar extinction coefficient
μ_a*	Absorption coefficient corrected for water content of brain tissue

LIST OF ABBREVIATIONS

fNIRS	Functional Near Infrared Spectroscopy
OSA	Obstructive Sleep Apnea
IYKOS	İşlevsel Yakın Kızıl Ötesi Spektroskopi
OSAS	Obstructive Sleep Apnea Syndrome
NREM	Non-rapid Eye Movement
REM	Rapid Eye Movement
EEG	Electroencephalography
AI/HI	Apnea Hypopnea Index
BMI	Body Mass Index
EOG	Electroocculography
EMG	Electromyography
ECG	Electrocardiography
CBF	Cerebral Blood Flow
CSF	Cerebrospinal Fluid
CBV	Cerebral Blood Volume
CytOx	Cytochrome Oxidase
Std. Dev	Standard Deviation

1. INTRODUCTION

Repetitive episodes of airflow reduction caused by pharyngeal narrowing resulting in acute gas exchange abnormalities and sleep fragmentation, are the basic characterization of obstructive sleep apnea syndrome (OSAS). OSAS can cause neurobehavioral and cardiovascular consequences [1]. Obesity, increased neck circumference, craniofacial abnormalities, hypothyroidism, and acromegaly are the risk factors for sleep apnea [2]. An apnea-hypopnea index of 5 or higher in association with daytime somnolence can define the obstructive sleep apnea syndrome. 4 percent of men and 2 percent of women between 30-60 years of age suffer from OSAS [2].

The standard procedure for the diagnosis of sleep apnea is called polysomnography test, in which sleep is recorded and the stage of sleep is determined by electroencephalography, electrooculography, and electromyography with other clinical parameters like arterial saturation of oxygen (SaO_2), respiration and pulse.

In this study, measurements were taken on the sleep apnea patients with the functional near infrared spectroscopy system which is developed in Bogazici University, Biomedical Engineering Institute, Biophotonics laboratory; that can measure the oxygen stress in prefrontal cortex by the help of the probe placed on the forehead area. During these measurements the clinical data of the patients were also be recorded. The ultimate aim was to identify clinically significant parameters derived from fNIRS measurements that will correlate highly with clinical measurements.

2. THEORY

2.1 Sleep Physiology

Sleep is determined as a state of unconsciousness in which the brain is relatively more responsive to internal stimuli than to external stimuli and it occupies one third of our existence. Sleep can be distinguished from other states of unconsciousness with the features such as the predictable cycling of sleep and the reversal of relative external unresponsiveness [3]. Sleep has effects on most fundamental homeostatic mechanisms (4).

Sleep affects and in turn is affected by almost every physiological and psychological process. It is necessary for our mental and physical health. Disturbances of sleep result in a variety of debilitating sleep disorders; they also exacerbate other illnesses. Studies have shown that sleep has functions such as restoration and recovery and energy conservation. Biochemical and physiological processes that are progressively decreased during wakefulness are restored during sleep. This hypothesis is supported by the increase of growth hormone secretion during sleep in humans and baboons. The metabolic rate and body temperature in endothermic animals, mammals and birds are reduced during sleep. Thermoregulatory and electrophysiological continuities between hibernation and sleep are the strongest data in favor of the energy conservation hypothesis. Hibernation represents an extension of physiological processes initiated during sleep. When animals fall asleep their metabolic rates decrease by about 10% and heat is dissipated from their bodies through peripheral vasodilation, which leads to a 1-2°C reduction in body temperature. This reduction in body temperature is controlled through the reduction, at the onset of sleep, in the thermo sensitivity of neurons of the peoptic nucleus of the hypothalamus below their prior waking threshold. This nucleus acts like a thermostat in the brain. When small mammals enter hibernation, they lower their body temperatures while remaining asleep, and continue to show predominant patterns of non-rapid eye movement (NREM) sleep during hibernation [5].

2.1.1 Sleep Cycle

Sleep is divided into a 90 minute cycle of Non Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep. This cycle is repeated 3-6 times during the night (6). In successive cycles the amount of NREM sleep decreases and the amount of REM sleep increases. Each state is comprised of a constellation of biological patterns of activity [5].

Brain stem, thalamus, hormones produced by the hypothalamus and external stimuli regulate the cycle of sleep and wakefulness [7].

According to Electroencephalographic (EEG) and polysomnographic recordings there are, five well defined stages of sleep.

Stage I is a transition between sleep and wakefulness which is usually only five minutes in duration. Short dreams may occur, usually involving images remembered from throughout the day. The brain's electrical activity slows as exhibited by tetha-rhythms on the EEG. *Stage II* is a somewhat deeper level of sleep, characterized by slower breathing and heart rates. The EEG of stage II shows slow tetha-rhythms, interspersed with periods of fast alpha-rhythms called sleep spindles and some delta-rhythms. About fifty percent of all sleep in a given night is Stage II. *Stages III and IV* are the deepest levels of sleep and have the slowest waves as measured by EEG: Stage III has both theta and delta rhythms, while Stage IV has only delta-rhythms. The body uses this time to maintain and restore itself. Growth hormone secretions are at their highest during these stages. Stages III and IV begin after one has been asleep for approximately one half hour. The first episodes of Stage II and IV sleep are usually the longest of the night. As successive cycles of sleep pass, these stages are replaced by longer periods of Stage V sleep.

Stage V is remarkably different from the previous stages. The brain and body become active, increasing heart rate and blood pressure. The eyes shudder quickly back and forth, giving this stage the name Rapid Eye Movement (REM) sleep. EEG patterns for REM sleep are much like those during wakefulness, and include many fast beta-rhythms. It may even be that the brain works harder during REM sleep than when awake. REM sleep

usually lasts anywhere from 11 to 25 minutes, typically longer in the later sleep cycles of the night. Approximately 25% of all sleep is REM sleep in adults, in children it is even higher. On completion of a phase of REM sleep, the brain and body return to Stage I, and begin another sleep cycle [6-8].

2.2 Obstructive Sleep Apnea

Repetitive episodes of airflow reduction caused by pharyngeal narrowing and results with acute gas exchange abnormalities and sleep fragmentation, are the basic characterization of obstructive sleep apnea syndrome (OSAS). OSAS can cause neurobehavioral and cardiovascular consequences [1]. Abnormal breathing, snoring, frequent awakenings and oxygen desaturation are involved in OSAS [9]. OSAS can be defined by apnea-hypopnea index (AI/HI), (number of apneas and hypopneas per hour of sleep), of 5 or higher in combination with daytime somnolence. According to these criteria, sleep apnea occurs in 4 percent of men and 2 percent of women who are 30 to 60 years of age. A much higher percentage meet at least one of these criteria: 16 percent of men and 22 percent of women have hypersomnolence, and 24 percent of men and 9 percent of women have an apnea-hypopnea index of at least 5. The index can exceed 100 in patients with very severe cases [2].

Three kinds of apnea have been described since the first case in 1965. Different from obstructive sleep apnea; in central apnea, the brain can not send the necessary signals to the breathing muscles to start respirations. This kind of sleep apnea is not common. The third kind of apnea is mixed apnea; which is combination of both central and obstructive apneas.

2.2.1 Risk Factors for OSAS

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Obesity, gender and age are the well documented epidemiological factors associated with obstructive sleep apnea (OSA).

60–90% of OSA patients evaluated in sleep clinics have a body mass index (BMI) greater than 28 kg/m^2. The distribution of fat further modifies the correlation between OSA and

obesity. Central obesity particularly involving the neck is predictive of those with greatest risk of OSA. The obesity is thought to affect the airway size through deposition of fat in the neck or external compression. It has been shown that, the effect of obesity is to be fourfold stronger than the influence of age and twice as strong as the influence of gender in predicting breathing disorders in the elderly.

OSA is a disorder with male preponderance. The male/female ratio ranges between 2–3:1 in the general population compared to the 10:1 to 90:1 ratios from clinic based studies. Females with OSA have higher BMI than males to manifest similar severity of symptoms. The difference in the prevalence of OSA between males and females is not clear. Sex hormones especially androgens are thought to modulate the development of OSA. There are several reports of exogenous androgens in either men or women precipitating OSA in individuals without previous history of sleep disordered breathing. Furthermore, an increased prevalence of OSA in obese women with polycystic ovary syndrome; a disorder characterized by excess androgens. The evidence from gender differences in anatomy, pharyngeal dilator muscle and ventilatory control mechanism is not conclusive. However, polysomnographic findings have shown specifically that women have lower apnea-hypopnea index scores than men during NREM sleep but similar scores during REM sleep. This suggests that whatever protects the women from upper airway collapse during NREM disappears in REM sleep. In REM sleep, muscle tone is abolished but the current evidence in tissue characteristics cannot explain this observation.

Sleep apnea is prevalent with increasing age. It is more common in the fifth through seventh decade of life. The increased incidence in the elderly may be related to the presence of other comorbidities. Young age seems to be protective against OSA by preventing airway collapse [1, 2,10].

2.2.2 Symptoms and Physical Characteristics Associated with OSAS

Well known symptoms of OSA can be listed as; persistent snoring, sudden awakenings accompanied by choking, apneas as observed by the bed partner and excessive sleepiness during daytime. This list can be improved by some of the other symptoms which

are not very specific such as; gastro-esophageal reflux, reduced ability to concentrate, memory loss, personality changes, mood swings, night sweating, nocturia, dry mouth in the morning, restless sleep and morning headache in adults. Hyperactivity, aggression and behavioral disturbance, frequent colds and coughing and odd sleeping positions in children can also be related with OSA [11].

Abnormal anatomy and increased collapsibility of the upper airway to defective airway reflexes are one of the most important factors which interact to produce OSA. Pharyngeal narrowing causes decreased upper airway muscle activity with sleep.

The ensuing rise in upper airway resistance increases transmission of the inspiratory negative intrathoracic pressure. This results in airway obstruction. Hypercapnia and hypoxia leads to arousal and pharyngeal opening due to increase in upper airway muscle activity. The improved airflow decreases carbon dioxide tension and better oxygen saturation [10].

Oedematous or long soft plate or uvula, hypertropic tongue tonsils, narrow oropharyns, adiposity or large neck circumference, maxillary hypoplasia are the other physical characteristics of OSA [11].

2.2.3 Consequences of OSAS

Obstructive sleep apnea syndrome can lead to a loss in quality of life. Neurobehavioral, social, cardiovascular, perioperative and postoperative consequences of OSAS make this syndrome a serious and important disorder, which has to be diagnosed and treated carefully.

One of the most important and specific features of OSA are excessive daytime sleepiness, impaired vigilance, mood disturbances and cognitive dysfunction. These features create a big risk for social life such as increased risk of motor vehicle crashes, occupational injuries and decreased quality of life.

Obstructive sleep apnea causes performance reduction during neurophyschological testing. Studies have shown that with a frequency of 15 apneas-hypopneas per hour of sleep, the decrement is equivalent to that associated with 5 years of aging [1].

Hypertension and cardiovascular diseases are more often seen in patients with OSA than do other patients [11]. The intermittent hypoxia, negative intrathoracic pressure variations, and arousals characteristic of apneas and hypopneas lead to acute increases in blood pressure at the termination of disordered breathing events, evolving into sustained hypertension via chronically heightened sympathetic nervous system activity and arterial baroreceptor dysfunction [1]. Mortality is increased with untreated OSA in patients with cardiovascular and cerebrovascular disease [1].

The syndrome is associated with vascular risk factors and with substantial cardiovascular morbidity and mortality. Several studies have shown a prevalence of the syndrome among patients with stroke that exceeds 60 percent, as compared with 4 percent in the middle-aged adult population [12].

Obstructive sleep apnea can increase the perioperative risk in patients. Endotracheal intubation can be more difficult in such patients and forced supine sleep positioning and analgesics can result in upper airway narrowing postoperatively [1]. Two anatomical landmarks have been shown to be important in patients with obstructive sleep apnea: an inferiorly positioned hyoid (distance between chin and hyoid bone) and increased length of the soft palate [11].

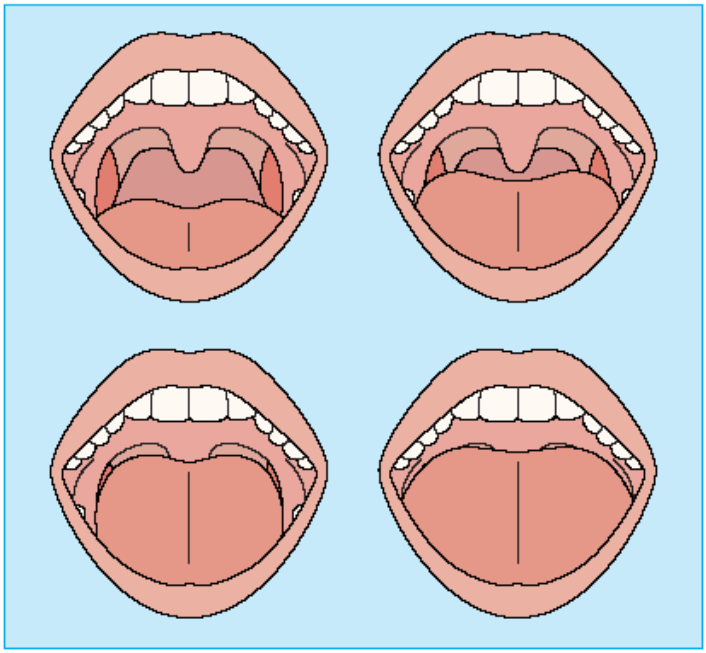


Figure 2.1 Physical characteristic of OSA: The size of the tongue is assessed in relation to that of the soft palate, while the tongue rests in the floor of the mouth. Stage 1 (top left): complete visualization of the uvula, tonsils, and arches. Stage 2 (top right): complete visualization of the uvula; the tonsils and arches are partly invisible. Stage 3 (bottom left): only the soft and hard palate are visible; the uvula is hidden. Stage 4 (bottom right): only the hard palate is visible [11].

Patients with obstructive sleep apnea are at high risk of developing postoperative complications when having surgery or other invasive interventions under general anaesthesia. This holds true for both surgery related to obstructive sleep apnea and unrelated surgery [11].

2.2.4 Diagnostic Test for OSAS-Polysomnography

Polysomnography is the recommended diagnostic test for breathing disorders related with sleep. Electroencephalography, electro-oculography, and electromyography; respiratory activity by nasal and oral airflow or pressure, thoracoabdominal inductance plethysmography, and oximetry; electrocardiography; limb movements by lower extremity electromyography; and body position are the modalities recorded during sleep with polysomnography. Polysomnograph machine converts these electrical impulses in the body to a graphical waveform. Sound meter to detect snoring, end tidal carbon dioxide

determination when OSAS is being investigated in children, and, rarely, esophageal pressure monitoring if central sleep apnea is suspected; may additionally be used in polysomnography tests [1].

By electroencephalography, electrooculography, and electromyography, the stage of sleep is determined; electrical activity in the brain during the different stages of sleep is distinctly different from that while awake. The EEG allows the physician to see if the patient is reaching all the stages of sleep to the appropriate depth and if the patient is being aroused excessively from these stages. Electrodes are also taped to the skin near the outer edges of the eyes to record data for an electrocculogram (EOG). This tells the examiner where the patient is in rapid eye movement sleep (REM). A device is placed near the patient's nose and mouth to measure airflow. Electrodes are connected to an electromyogram (EMG) and taped or pasted on the patient's chin to detect activity in the jaw muscles. The EMG detects the presence of REM sleep when the jaw muscles relax.

Special belts are placed around the patient's chest and abdomen to detect and record the rising and falling movements associated with the respiration. A pulse oximeter, a noninvasive device for measuring blood oxygen content, is attached to the finger, and electrodes to provide an electrocardiogram (ECG) are attached to the chest to measure heart rate. The episodes of apnea and hypopnea are defined by a clear reduction in airflow or tidal volume, often accompanied by a decrease in oxygen saturation and terminated by an arousal (an interval of three seconds or longer in which the electroencephalographic pattern indicates that the patient is awake) [2, 13].

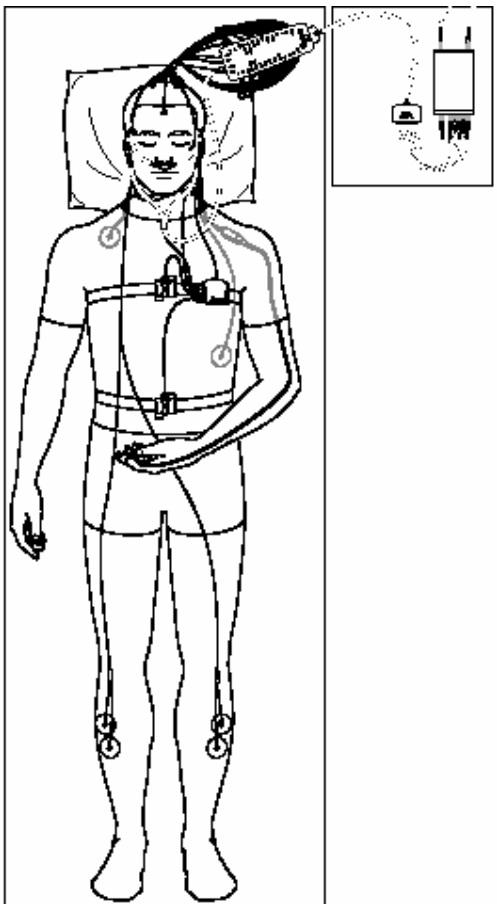


Figure 2.2 Schematic diagram of a subject during polysomnography recording [13]

2.3 Functional Near Infrared Spectroscopy

The basis for functional near infrared spectroscopy (fNIRS) is the ability of light to penetrate several centimeters into tissues and the absorption spectra of oxy-hemoglobin (HBO_2) and deoxy-hemoglobin (HB), in the wavelength range of 700-900 nm [14].

Near infrared light between 700nm to 1300 nm penetrates skin and skull [15]. With this technique, changes in the concentration of tissue oxy-hemoglobin and deoxy-hemoglobin can be measured non-invasively [16]. Changes in relative amounts of Oxy-hemoglobin and deoxy-hemoglobin can be calculated by applying absorbance changes of two or more near-infrared wavelengths into the equations obtained from in vitro studies [15]. Cerebral blood flow (CBF) can also be estimated by using fNIRS for quantifying

haemodynamic states non-invasively [16]. Changes in oxygen delivery and consumption can be assessed with the changes in oxy and deoxy-hemoglobin within the tissue [15].

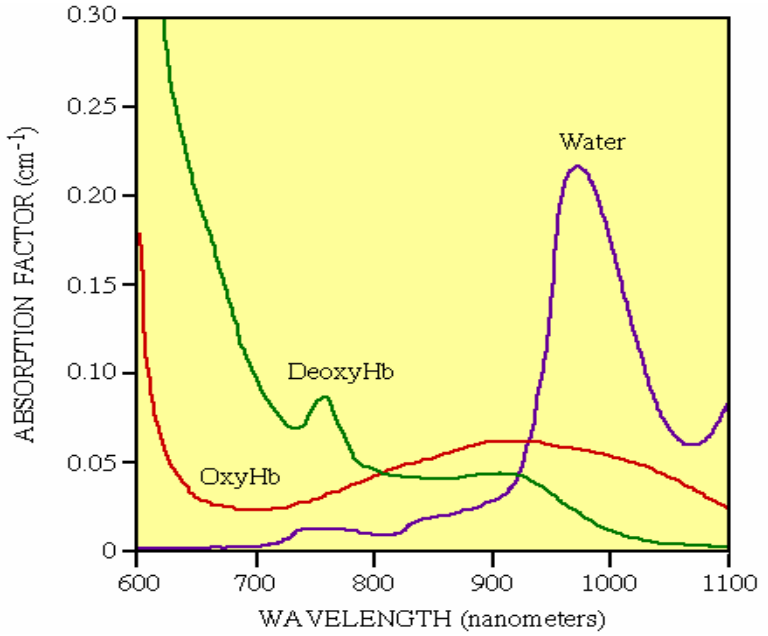


Figure 2.3 Absorption spectra of HBO_2, HB and Water [19]

Functional brain imaging based on deterministic signals measures changes in reflectance of the cortex as a result of small changes in the optical properties of electrically and/or metabolically active brain tissue. One of the sources for the activity-dependent deterministic signal is a small change in the color of the tissue, produced by changes in the concentration of deoxy-hemoglobin and oxy-hemoglobin within the capillaries in response to the increased metabolic demand of active neurons. The absorption spectra of oxy-hemoglobin (HbO_2) and deoxy-hemoglobin(Hb) differ significantly for near infrared light between 750 nm and 1000 nm (Figure 2.3). By imaging the activity using these wavelengths for hemoglobin absorption it is possible to estimate the contribution of those components to the signal [17-19].

It has been thought that, layered structure like in the head as skin/scalp-skull-cerebrospinal fluid (CSF)-cerebral tunics- brain, can affect the optical penetration depth. The results of the studies on near infrared spectroscopy have shown that the contribution of

the superficial layers of the head to the NIRS output signal is negligible due to much greater absorption and scattering changes in the deeper layers like gray matter [14].

Measurement of specific biochemical markers, localization to a fairly superficial layer of gray matter and a rapid response are the advantages of fNIRS of brain over other imaging techniques (20). Another potential advantage of near infrared spectroscopy is that, it does not require pulsatile blood flow like in pulse oximetry [21].

Owing to its non-invasive nature, fNIRS can be used for extended periods of time. It is much more inexpensive compared to other imaging techniques and it is small and portable [20].

2.4 Studies on Obstructive Sleep Apnea with Functional Near Infrared Spectroscopy

The first fNIRS study was performed by Jöbsis in 1977 and this was followed by others.

The first application of fNIRS to OSAS patients was performed by Hayakawa et al. (1996). In this study; eight patients were studied. Standard polysomnography was performed synchronously with the functional near infrared spectroscopy instrument, in which the optode and pickup were fixed on the dominant side of the forehead 3 or 4 cm apart to get global information in the frontal region of the dominant hemisphere. The source to detector distance was 3.5 cm.

As a result of the study, for all apneic episodes a consistent decrease in oxy-hemoglobin and increase in deoxy and total hemoglobin were seen for all apneic episodes (15). Hayakawa et al discussed that, these findings can be used to explain the cerebral blood volume (CBV) increase during apnea; hence total hemoglobin can be used as an indicator of changes in blood volume in fNIRS technique. While CBV increased, the oxygen supply to the brain decreased. This can prove that increase in CBV cannot compensate for reduced arterial oxygen saturation so that cerebral tissue hypoxia may occur during apnea [15].

The other application of fNIRS to OSAS patients was performed by Safanova et al.(2003). In this study eight patients with OSA and thirteen subjects as controls were studied simultaneously with a pulse oximeter which measures arterial oxygen saturation (SaO_2) and heart rate, and a strain gauge for measuring the breathing rate. A multi – distance approach in fNIRS with four source to detector distances ranging between 1.98-4.08 cm were used to assess cerebral tissue oxygenation and hemodynamics in obstructive sleep apnea sufferers.

OSA subjects were compared with the control group during a breath holding exercise. An increase in oxy-hemoglobin and a decrease in deoxy-hemoglobin were seen in control group in breath holding exercises which is typical to cerebral auto regulatory response. In contrast, severe brain deoxygenation and seriously compromised brain auto regulation in the OSA subjects were seen with a decrease in oxy-hemoglobin and increase in deoxy-hemoglobin. In OSA subjects during daytime napping an increase in total hemoglobin and oxy-hemoglobin were detected during apnea which is a sign for protective cerebrovascular response to hypoxia and hypercapnia due to vasodilation and opening of capillary bed consisting with an increase of cerebral blood flow [14].

Reece et al. applied near-infrared spectroscopy to estimate cerebral hemodynamics in conscious and anaesthetized adult subjects in 1996 with a result of inability to demonstrate a significant effect of general anaesthesia on cerebral blood flow with the present technique [16].

Cytochrome oxidase (CytOx) redox state during OSAS was measured with NIRS by McGown et al. in 2003. Small changes in CytOx redox state were observed, which correlate with changes occurring in cerebral tissue saturation, SaO_2 and CBV [22].

3. METHODS OF THE STUDY

3.1 Instrumentation

A standard polysomnography system (Flaga, Embla, Iceland), using Somnologica 2.0 software, involving, SaO_2 measurement with a pulse oximeter and breathing rate measurement with a respiratory strain gauge, EEG and EMG were used synchronously with fNIRS device, Niroxcope 201, developed at the Biophotonics Laboratory.

The functional near infrared spectroscopy (fNIRS) equipment developed consists of a probe that contains light sources and detectors, data collection unit and a computer program. 2.5 cm distance between the light sources and the detector allows measuring changes in the first 4-5 mm part of the brain cortex as studied by Delpy and Cope in 1997 [24]. It has 1.7 Hz sampling rate with ten detectors and sixteen source to detector distances.

The probe is placed on the forehead area and covers both hemispheres. Figures 3.1 and 3.2 show the NIROXCOPE system in the laboratory.

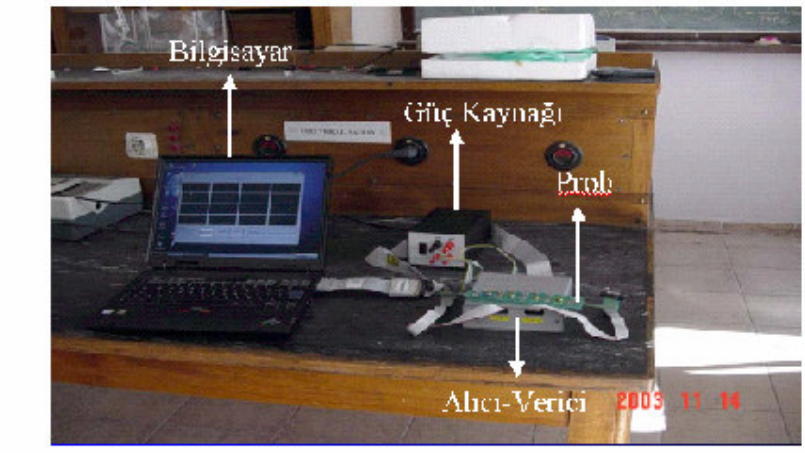


Figure 3.1 NIROXCOPE 201

Figure 3.2 a) NIROXCOPE 201 probe, b) Forehead application

3.2 Subjects

Six subjects suffering from OSA were used in this study. Five of them were male and one of them was a woman. The mean age of the subjects was 54 while the oldest was 60 and the youngest was 45. All of the subjects have apnea- hypopnea index (AI/HI) bigger than 10, while the maximum AI/HI index was 62 and the minimum was 15. One of the subject was having severe deoxygenation problem and pulmonary hypertension with an awake arterial oxygen saturation of 64 % and minimum SaO_2 of 44 % during sleep.

Table 3.1
Summary of subjects in the study.

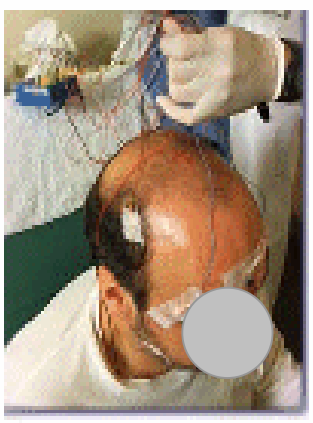
Subject	Sex	Age	AI/HI
1	M	47	62
2	M	56	22
3	M	45	45
4	M	60	17
5	M	58	62
6	F	58	15

3.3 Experimental Procedure

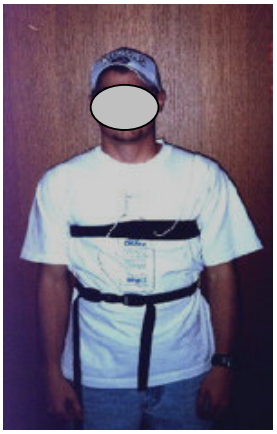
Three subjects were studied during nocturnal sleep and three subjects were studied during daytime sleep. Daytime sleeps were not like napping; they all slept longer than three hours.

Subjects were prepared for the recording half an hour before, standard polysomnography procedures were followed. By electroencephalography, electrooculography, and electromyography, the stage of sleep was determined. Respiration activity was recorded by thoracic and abdominal respiratory strain gauges and a nasal probe. SaO_2 was measured by a pulse oximeter. fNIRS probe was placed to the forehead area of the subjects. Both polysomnography and fNIRS systems were operated simultaneously. Recording start and finishing times were recorded both for polysomnograph and fNIRS system.

All subjects were informed about the measuring method and aim of the study.



(a)



(b)

Figure 3.3 a) Positioning of the EEG, EOG and EMG electrodes, b) View of a subject ready for polysomnography recording.

4. METHODS OF EVALUATION

Data analysis procedures of this fNIRS study include the processing of data collected simultaneously by 1) Polysomnography and 2) fNIRS NIROXCOPE 201 system. In both systems a basal record was taken after the placement of the electrodes and fNIRS probe, then the changes in physiological parameters were measured and quantified. The following physiological signals were evaluated for sleep apnea study:

The respiratory signal was processed to estimate the frequency of the respiratory rhythm to assess normal breathing and also to detect and count sleep apnea/hypopnea episodes, as well as to determine their duration. The recordings of the polysomnography system in Istanbul University Medical Faculty were taken in digital format and processed with Matlab program.

The changes in SaO_2 measured by pulse oximeter of the polysomnography system were analyzed with respect to hypoxia during sleep apnea. It is compared with the corresponding changes in cerebral tissue oxygen saturation (SO_2) calculated from fNIRS measurements.

Oxy-hemoglobin (HBO_2) and deoxy-hemoglobin (HB) concentrations were calculated from biooptical measurements obtained by NIROXCOPE 201 system with an algorithm which is developed institute Biophotonics laboratory, containing the following well known tissue equations for tissue hemoglobin parameters [14].

$$[\mathrm{HBO_2}] = \frac{\mu_a{}^*(\lambda_1)\varepsilon_{HB}(\lambda_2) - \mu_a{}^*(\lambda_2)\varepsilon_{HB}(\lambda_1)}{\varepsilon_{HBO2}(\lambda_1)\varepsilon_{HB}(\lambda_2) - \mu_{HBO2}(\lambda_2)\varepsilon_{HB}(\lambda_1)}$$

$$[\mathrm{HB}] = \frac{\mu_a{}^*(\lambda_1)\varepsilon_{HBO2}(\lambda_1) - \mu_a{}^*(\lambda_1)\varepsilon_{HBO2}(\lambda_2)}{\varepsilon_{HBO2}(\lambda_1)\varepsilon_{HB}(\lambda_2) - \varepsilon_{HBO2}(\lambda_2)\varepsilon_{HB}(\lambda_1)}$$

Where the brackets [ ] indicate the concentration of the chromophore; $\varepsilon HB(\lambda_1)$, $\varepsilon HB(\lambda_2)$, $\varepsilon HBO_2(\lambda_1)$, $\varepsilon HBO_2(\lambda_2)$ are the molar extinction coefficients of HB and HBO_2 at

wavelengths λ_1 and λ_2; μ_a* indicates absorption coefficients corrected for water content of brain tissue; $\mu_a^*(\lambda) = \mu_a(\lambda) - 0.7\ \mu_a^{H2O}(\lambda)$; where $\mu_a^{H2O}(\lambda)$ is the water absorption coefficient at wavelength λ.

Once the concentrations of oxy-hemoglobin and deoxy-hemoglobin are calculated, total hemoglobin (tHB) and SO_2 can be calculated with the following equations: [14]

$$[tHB]=[HBO_2]+[HB]\ ; \quad SO_2=100*[HBO_2]/[tHB]$$

The quantitative and qualitative changes were observed in $[HBO_2]$, [HB], [tHb] (μmol/L), and SO_2 (%) observed in OSA subjects These observations were made with manual calculations and also with the algorithms developed in the Biophotonics Laboratory.

We calculated the degree of blood and cerebral tissue deoxygenation by calculating the decreases in SaO_2 and SO_2.

The phase differences between respiratory signal, SaO_2, and cerebral tissue hemodynamics were calculated to evaluate the difference of the response times of brain tissue and blood to the apneic events.

The measurements were taken from the 8^{th} detector of fNIRS in order to have data from the middle of the forehead. We have decided not to investigate lateralization affects since hypoxia induces hemodynamic changes globally.

5. RESULTS AND DISCUSSIONS

Apnea detection during polysomnography recording is done by looking at the respiration activity and arterial oxygen saturation. If the respiration activity decreases 20 % it is called as hypopnea and an apneic event usually comes after a hypopnea with more than 50 % decrease in respiration activity and followed by a decrease in SaO_2.

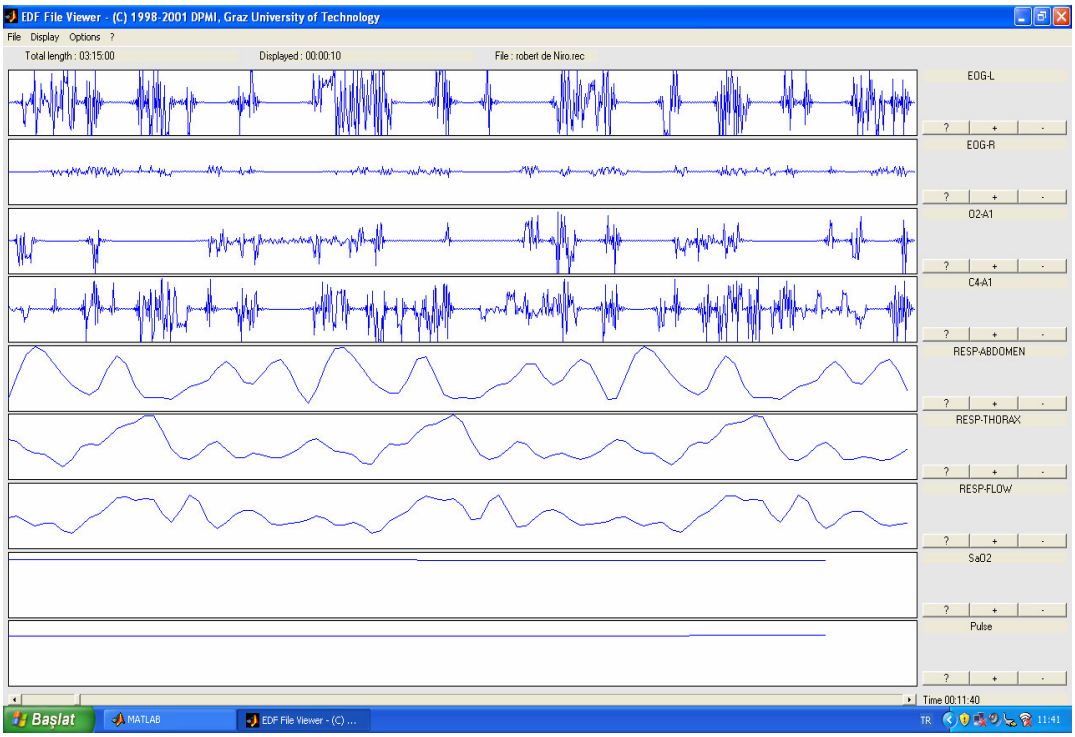


Figure 5.1 Standard screen of a polysomnography recording with channels of EOG, EEG, Respiration (abdomen, thorax, nasal), SaO_2 and pulse for 10 minutes

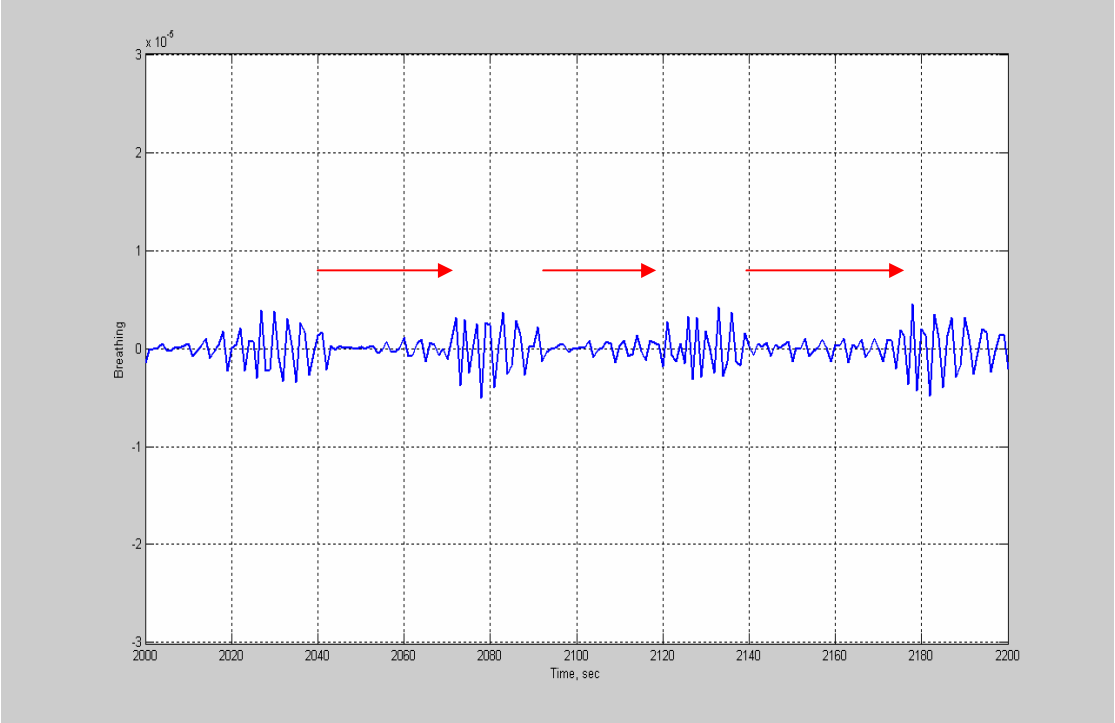


Figure 5.2 Breathing activity of a subject for 200 secs shows repetitive apneic events with red arrows

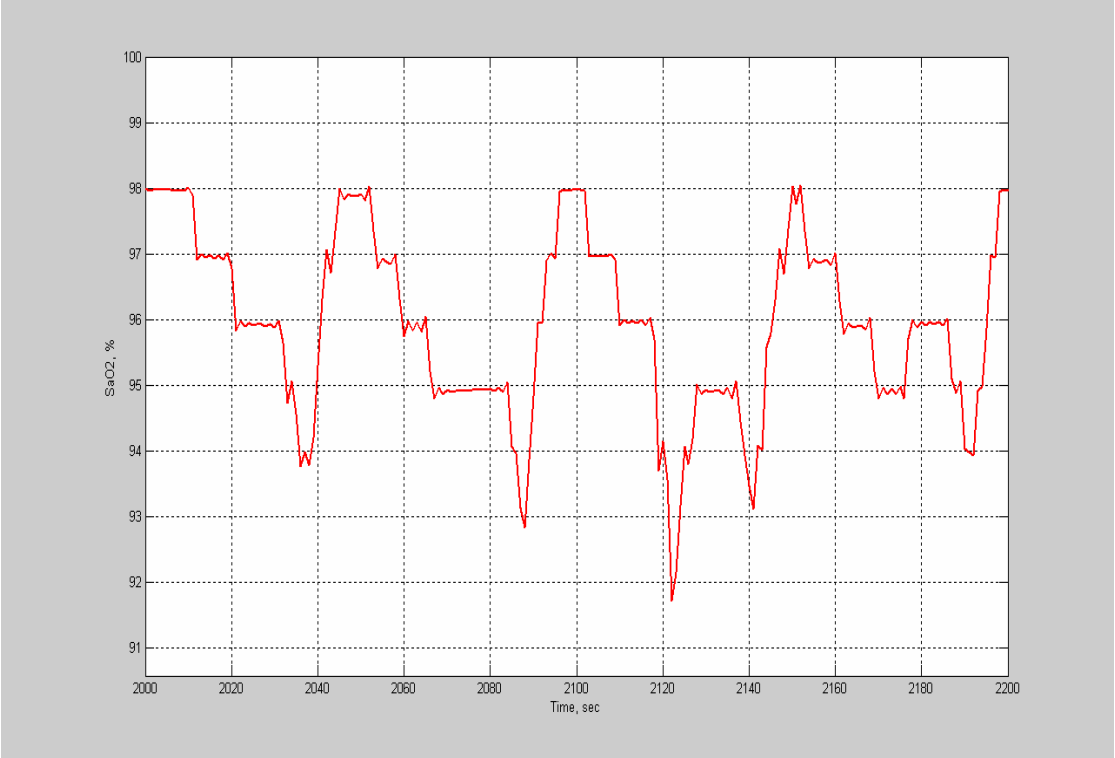


Figure 5.3 Change in SaO2 during repetitive apneas shown in figure 5.2

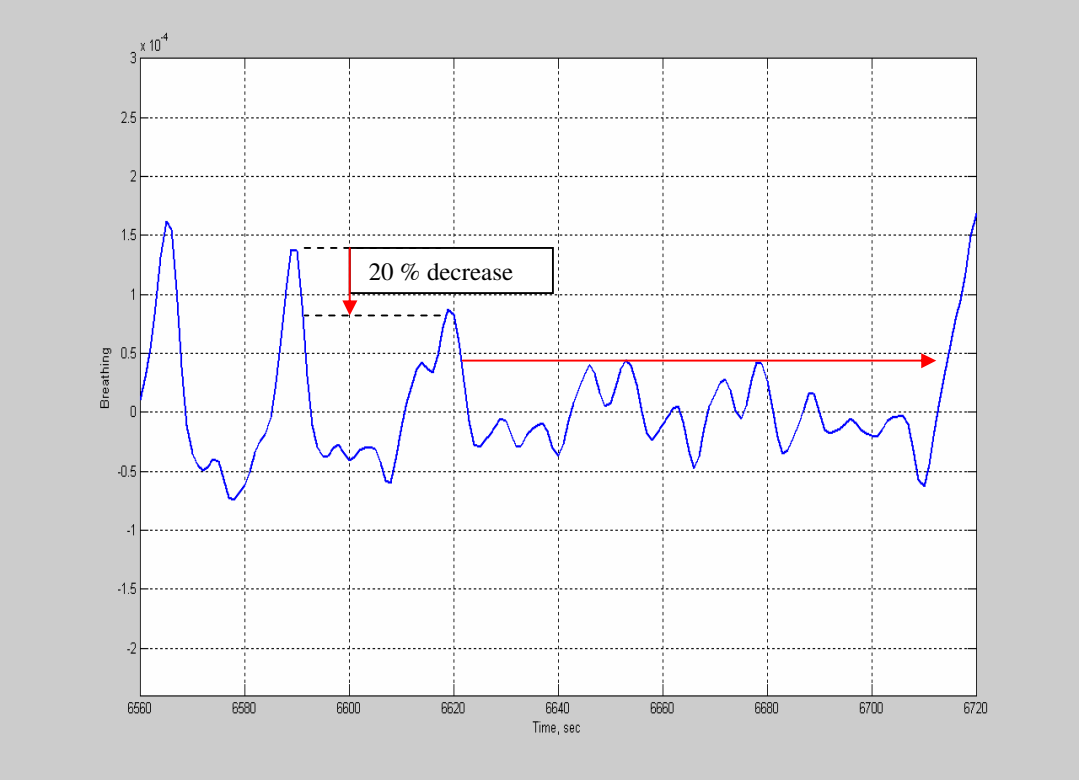


Figure 5.4 Breathing activity of a subject shows apnea event comes after a hypopnea event.

5.1 Deoxygenation in blood and cerebral tissue

Blood and cerebral tissue deoxygenations were calculated by analyzing the decreases in SaO_2 and SO_2 with respect to the baseline values. Baseline values for SaO_2 are the measured values of the subjects in resting condition before sleep and for SO_2 the base line values are taken as zero. These values are normalized by the duration of apnea period. Table 5.1 shows the deoxygenation levels in which t_a is the duration of apnea, $\Delta_n SaO_2 = \Delta SaO_2 / t_a$ and $\Delta_n SO_2 = \Delta SO_2 / t_a$.

Table 5.1
Summary of blood and cerebral tissue deoxygenation.

	t_a (sec)	**Mean $\Delta_n SaO_2$ (% / sec)**	**Mean $\Delta_n SO_2$ (% / sec)**
Mean	36,29	0,428	0,042
Std. Dev	20,86	0,419	0,056

As seen in table 5.1, deoxygenation in blood is more perceptible than cerebral tissue deoxygenation. A total of 38 apnea durations were taken into account, figure 5.1 shows the relationship between $\Delta_n SaO_2$ and $\Delta_n SO_2$ with R=0,696.

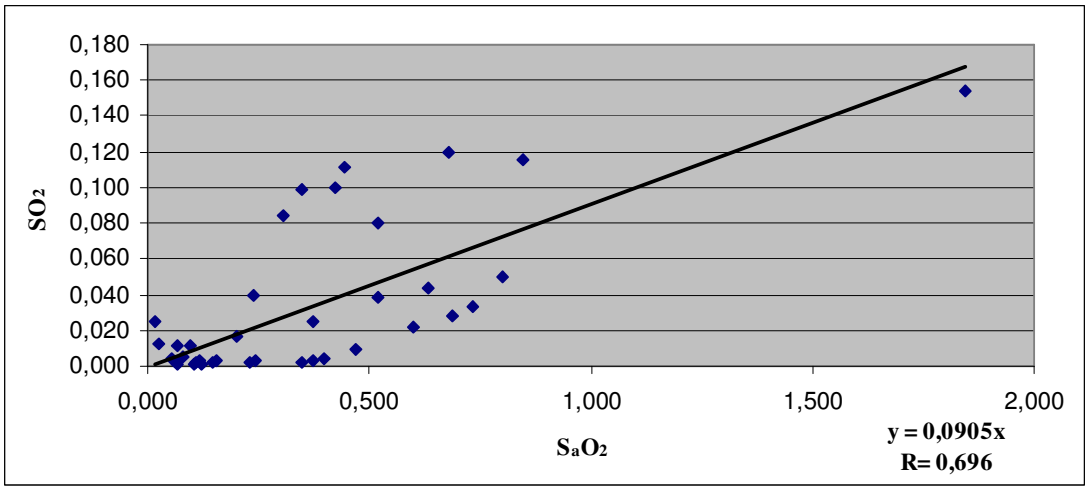


Figure 5.5 Relationship between $\Delta_n SaO_2$ and $\Delta_n SO_2$.

Safonova et al. (2003) have shown that cerebral tissue deoxygenation is less than the peripheral deoxygenation level for apneic episodes [14]. In accordence with this finding, in this study it has been shown that the decrease in cerebral tissue oxygenation is nearly ten times less than the decrease of blood deoxygenation measured with a finger probe. This can be explained by a protection mechanism of brain against hypoxia.

It has been known that apneic episodes are followed by hypercapnia, the dilation of arteries decrease cerebral resistance and increase cerebral blood flow [15]. This increase in cerebral blood flow works as a protection mechanism for brain from hypoxia. This is the reason for a less decrease in cerebral oxygenation. It has also been known that cardiac output decreases during apnea [15]. Normally the brain receives the 20 % of the cardiac output. If cardiac output decreases, than cerebral blood supply is maintained and the systemic circulation receives proportionally less oxygenated blood.

5.2 Changes in Cerebral Hemodynamics During Apnea

Apnea and hypopnea durations were chosen according to the apnea and hypopnea definitions. Hypopnea is as important as apnea in this study because it were aimed to see the changes in cerebral hemodynamics while there was a consistent decrease in breathing.

In subjects with obstructive sleep apnea but no other severe illnesses deoxy-hemoglobin and total hemoglobin show significant increases during apneic episodes as well as increase in oxy-hemoglobin with less amplitudes. Figures 5.6 and 5.7 show the changes in oxy-hemoglobin, deoxy-hemoglobin and total hemoglobin during apneic events.

Hayakawa et al. (1996) observed a consistent decrease in oxy-hemoglobin and increase in deoxy-hemoglobin and total hemoglobin for all apneic episodes [15]. In contrast to this finding, Safonova et al. (2003) have shown that, changes in oxy-hemoglobin and deoxy-hemoglobin due to sleep apnea/hypopnea events were not in opposite phase correlation but had a different time shift [14].

In accordance with the Safonova et al.'s study, consistent increase in deoxy-hemoglobin and total hemoglobin, and an increase in oxy-hemoglobin with a smaller amplitude observed in this study in the recordings of subjects with obstructive sleep apnea and no other severe diseases. This is a cerebrovascular response to hypoxia and hypercapnia with an increase of cerebral blood flow, where total hemoglobin can be used as an indicator for cerebral blood volume and flow. Brain can be protected from an injury during apnea by the help of this cerebrovascular response.

Total hemoglobin and deoxy-hemoglobin increased significantly with less a significant increase in oxy-hemoglobin, this means that the same amount of oxygen is carried with an increased amount of blood. Increased amount of blood in cerebral tissues can have a consequence such as an increase in cerebral blood pressure as Jennum and Borgesen (1989) observed where arterial blood pressure and central venous pressure increased at the end of apnea [23]. In severe cases with long apnea durations, the increase in intracranial pressure can lead to permanent brain damage.

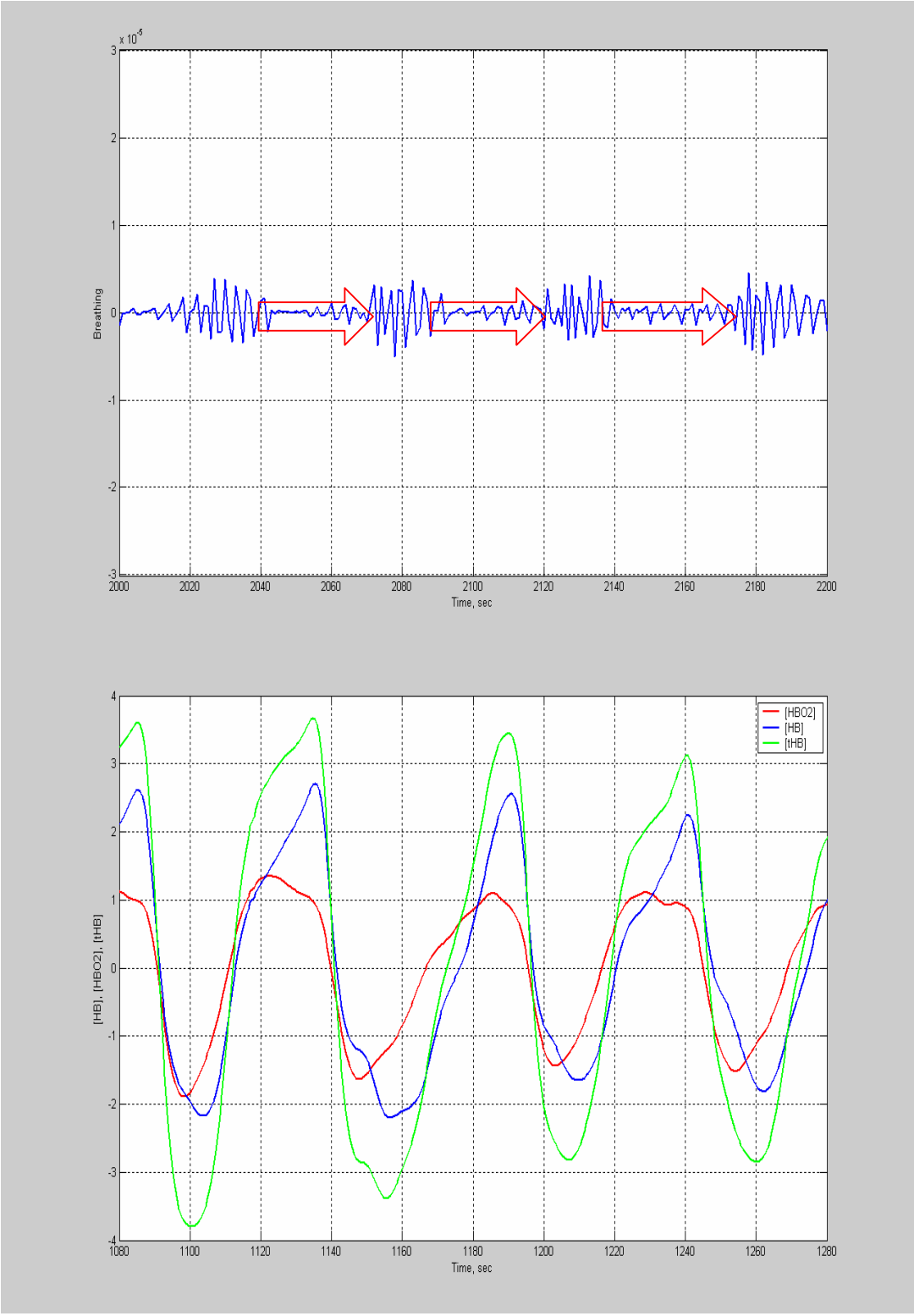


Figure 5.6 Changes in cerebral hemodynamics during repetitive apneic episodes.

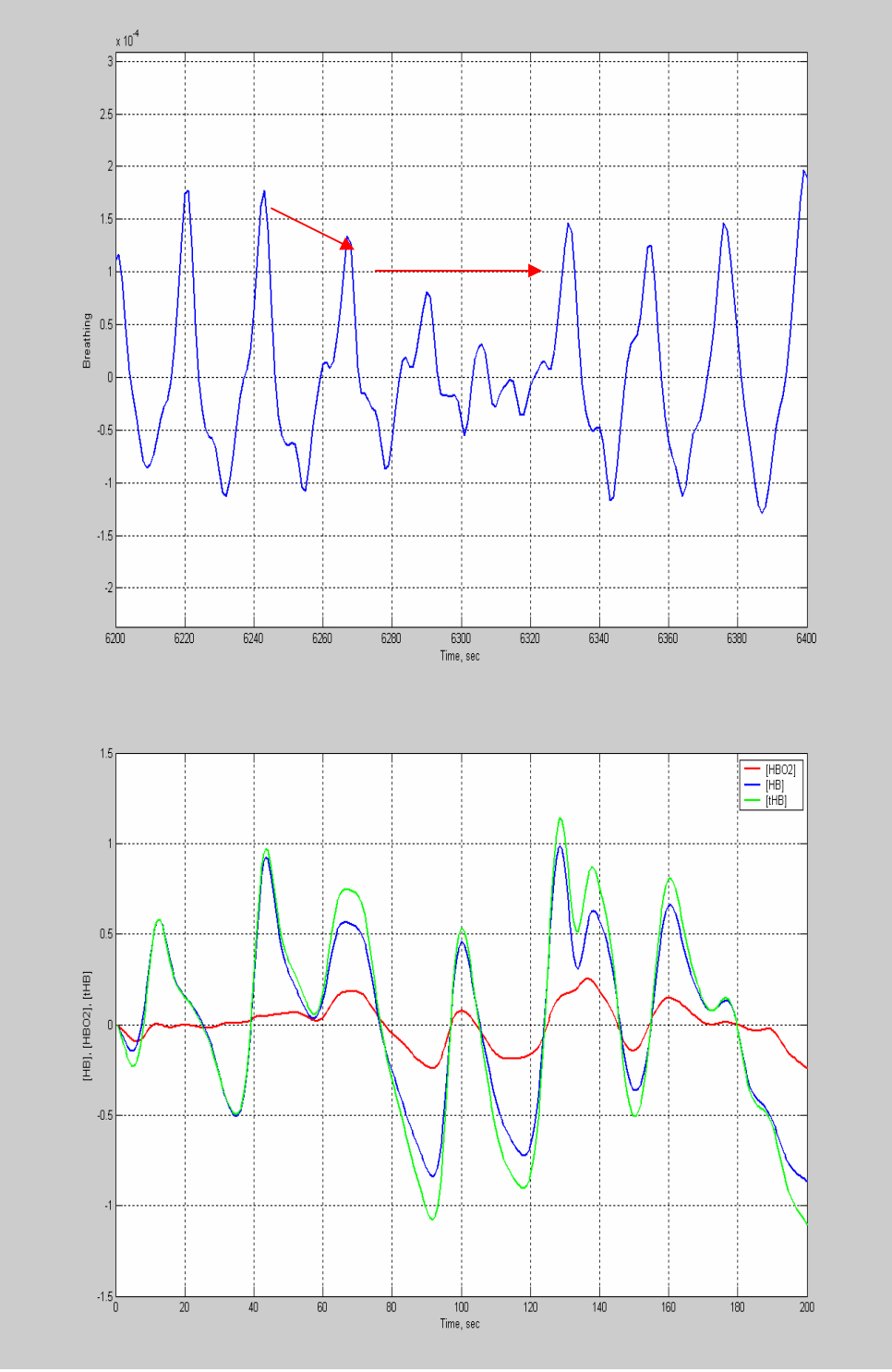


Figure 5.7 Changes in cerebral hemodynamics during an apneic episode

In one of the subject with severe deoxygenation problem and pulmonary hypertension with an awake arterial oxygen saturation of 64 % and minimum SaO_2 of 44

% during sleep, decrease in oxy-hemoglobin and increase in deoxy-hemoglobin and total hemoglobin were seen during significant reductions in breathing as shown in figure 5.8.

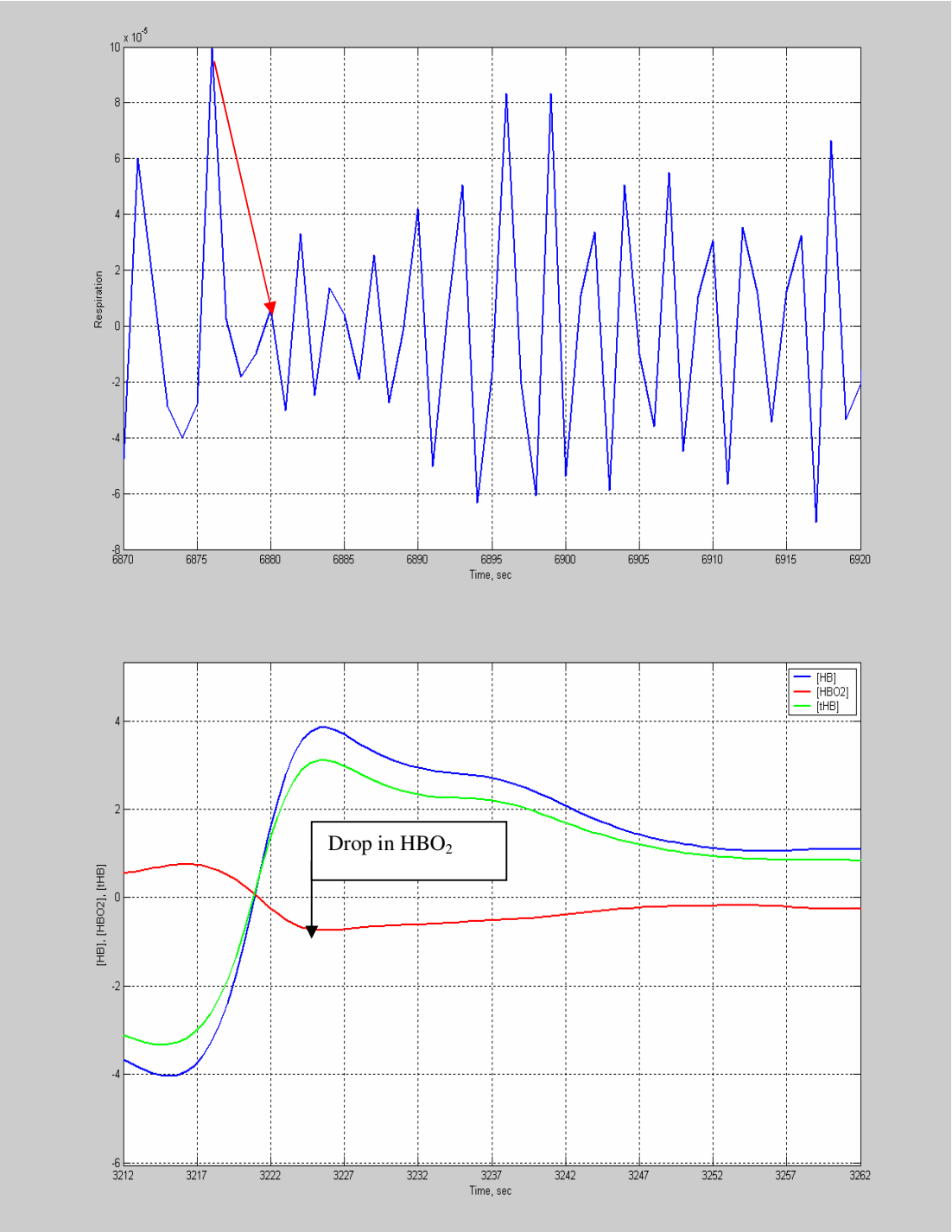


Figure 5.8 Changes in cerebral hemodynamics during a consistent decrease in breathing

In this case, total hemoglobin and deoxy-hemoglobin still increases, but as the subject normally has deoxygenation problem in daytime, cerebral oxy-hemoglobin cannot be increased.

5.3 Phase Differences

During data analysis, phase differences between respiration activity, SaO_2 and tissue hemodynamics were also studied. It was aimed to see how long it takes for peripheral and cerebral tissues to respond for an apneic event. It has already been known that arterial oxygen saturation can not respond to an apneic event immediately.

As shown in figure 5.9, apnea start moments were marked and the corresponding changes in SaO_2 and hemodynamics were examined.

Figure 5.9 shows that, arterial oxygen saturation responds for an apneic event as a dip in A_i after the respiration starts again. In contrast to this, increasing trend of hemodynamic parameters start before the breathing stops S_i and the peak values are seen in the middle of the apneic episodes. It is obvious that there are phase differences in the peaking of these differenr physiological events. We have computed this phase differences. This analysis was performed for a total of 37 different apneic episodes for six patients and the results are shown in table 5.2.

Table 5.2
Phase differences between respiration, SaO2 and hemodynamic parameters.
Mean values are calculated as Mean=1/n Σ (S_i-A_i), 1/n Σ (S_i-H_i), 1/n Σ (H_i-A_i)

	S_n-A_n	**S_n-H_n**	**H_n-A_n**
Mean (sec)	-37,038	22,709	59,747
Std. Dev	19,667	21,172	28,948

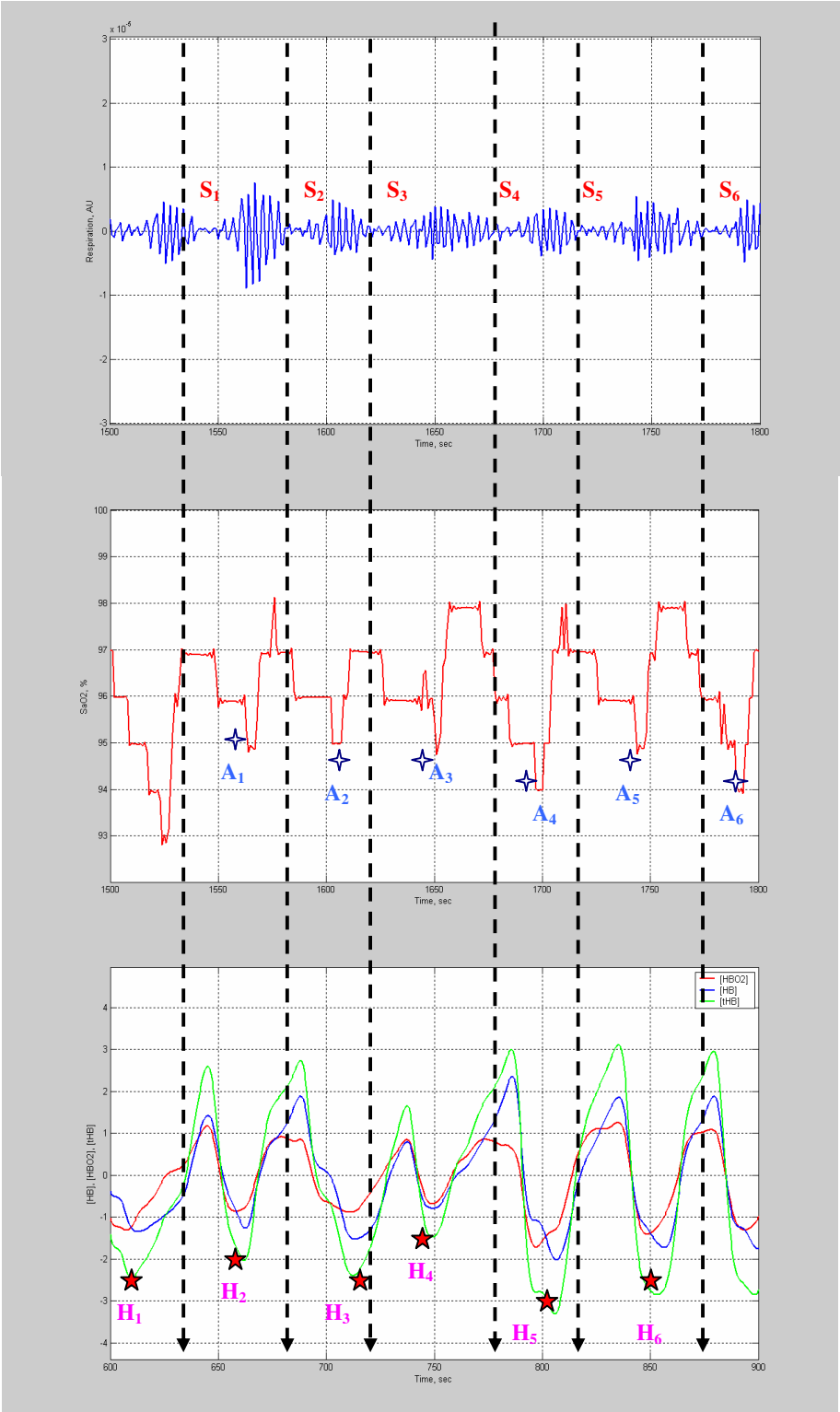


Figure 5.9 Phase differences analysis for repetitive apneic events where S_i: time of breathing stops, A_i: time for arterial desaturation and H_i: change in hemodynamic parameters measured with fNIRS

As seen in Table 5.2, arterial oxygen saturation responds for an apneic event with a delay of 37 seconds while the hemodynamic parameters H_i start to change 22 seconds in advance the breathing stops.

In Hayakawa et al.'s study (1996), it was mentioned that total hemoglobin peaked several seconds after the end of apnea [15]. Safonova et al. (2003) mentioned a different time shift between the changes in oxy-hemoglobin and deoxy-hemoglobin changes [14]. Both studies did not focus on a possible phase difference between respiration, arterial oxygen saturation and hemodynamics.

It is not surprising that peripheral tissues respond to an apneic event in several seconds. It would not be surprising if the cerebral tissue responds to an apnea faster than the peripheral tissues. In this study, it has been discovered that cerebral hemodynamics start changing before breathing activity stops.

The physical mechanism that preserves the cerebral oxygen supply detects very little oxygenation changes during hypopnea (before apnea) and overshoots in its correction. In any case, there is a finite capacity for correction of oxygenation which would account for the peaking during the apneic events. It is possible that, as well as hypercapnia, the reduction in the HBO_2 is necessary to restart respiration.

6. CONCLUSION

In this study we aimed to measure changes in cerebral tissue oxygenation and hemodynamics during obstructive sleep apnea by near infrared spectroscopy, which is a non-invasive and easy to use instrument during sleep.

A near infrared spectroscopy device, called Niroxcope 201, which was made in Bogazici University, Biomedical Engineering Institute, Biophotonics Laboratory, was used during the study in combination with a commercial polysomnography system.

It was observed that, during apneic events, cerebral tissue deoxygenation was not as significant as deoxygenation in peripheral tissues. In accordence to this finding, it can be told that brain has an auto regulation as a preventive mechanism against hypoxia. In this study, during apneic events, increases in deoxy-hemoglobin and total hemoglobin were observed in combination with a less increase in oxy-hemoglobin. As total hemoglobin can be used as an indicator of cerebral blood volume, it can be assumed that cerebral blood volume increases during apneic episodes. This is again a cerebrovascular response to hypoxia.

Total hemoglobin and deoxy-hemoglobin increased significantly with a less significant increase in oxy-hemoglobin, which means that the same amount of oxygen is carried with an increased amount of blood. Increased amount of blood in cerebral tissues can have a consequence such as an increase in intracranial blood pressure.

Another fact that was observed in this study was the phase differences between respiration, SaO_2, and hemodynamic parameters during apneic episodes. As known before, this study also proved that SaO_2 shows a response for an apneic event after several seconds. The surprising result was the phase difference between respiration and hemodynamic parameters. Early changes in hemodynamic parameters that came before breathing stopped, were observed in this study.

As a future work, these phase differences should be investigated carefully with a large number of subjects to see if there is a different phenomenon in OSA patients which

occurs in brain and results with a decrease in breathing activity. Continuous blood pressure should also be monitored to detect if there is an increase of this parameter during apneic events.

Working with patients during sleep poses challenges for neuro-imaging techniques. Near infrared spectroscopy is a non-invasive technique which is easy to use during sleep. Niroxcope 201 probe used in this study can be improved and miniaturized for easy stabilisation on head during sleep.

With near infrared spectroscopy in combination with polysomnography, a method of evaluating intracerebral hemodynamic activity is achieved. Clinicians can benefit from this device for investigating the cerebral tissue oxygenation and hypoxia during sleep apneas. This technique can also be used as a monitoring system to measure cerebrovascular hemodynamic changes in other clinical areas such as operating rooms to observe the cerebrovascular abnormalities under anaesthesia.

APPENDIX A. POLYSOMNOGRAPHY and fNIRS MEASUREMENTS

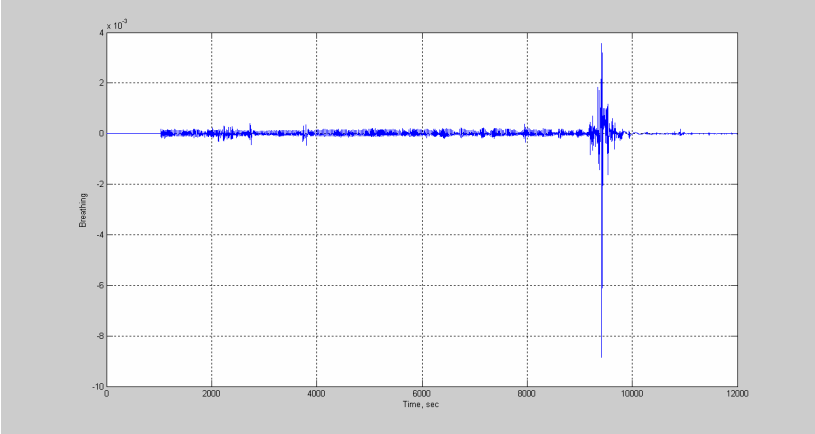


Figure A.1 Respiration signal of subject RDN for the whole recording of 200 minutes duration. The high amplitude signals observed around 9500 sec. are due to motion artifact

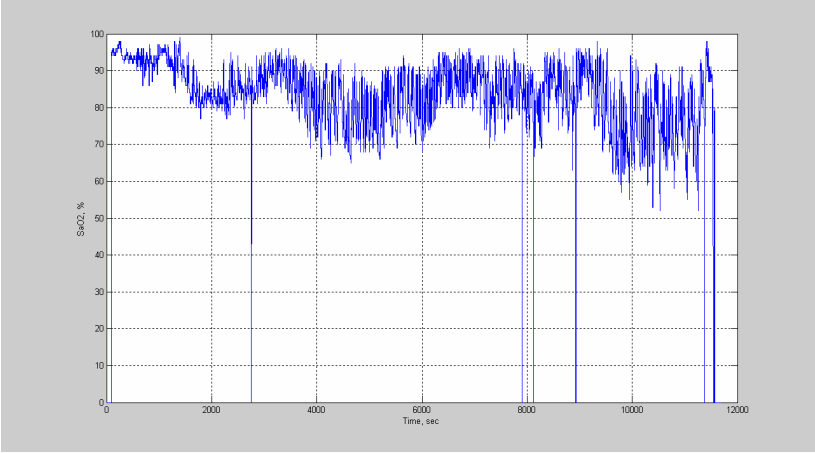


Figure A.2 Arterial oxygen saturation signal of subject RDN for the whole recording of 200 minutes. The zero values observed around 3000, 8000 and 12000 secs. are because of disconnection of the finger probe

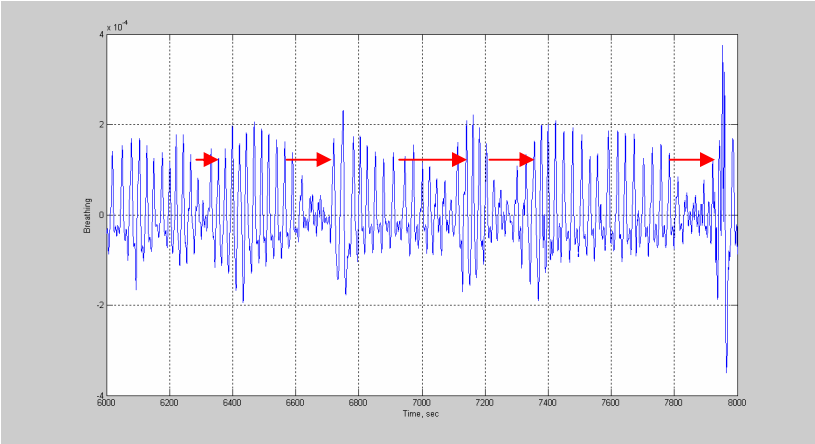


Figure A.3 Breathing activity of subject RDN for half an hour as a zoomed version of Figure A.1 with apneic episodes marked with arrows

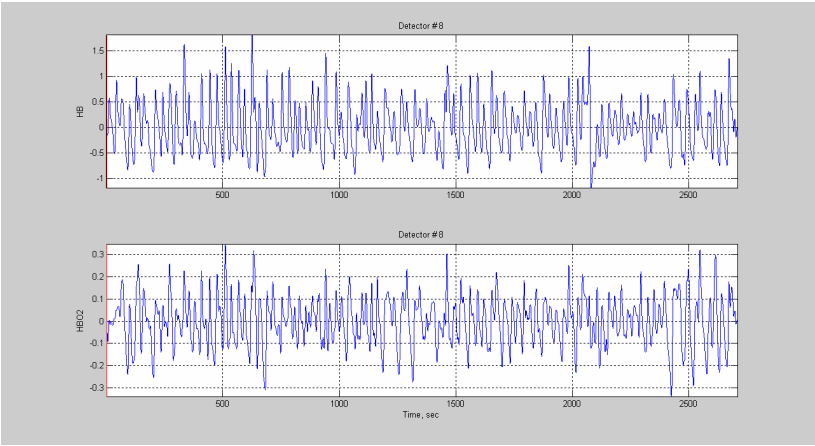


Figure A.4 Oxy-hemoglobin and deoxy-hemoglobin changes in cerebral tissue of the subject RDN for the whole 2 hrs. recording

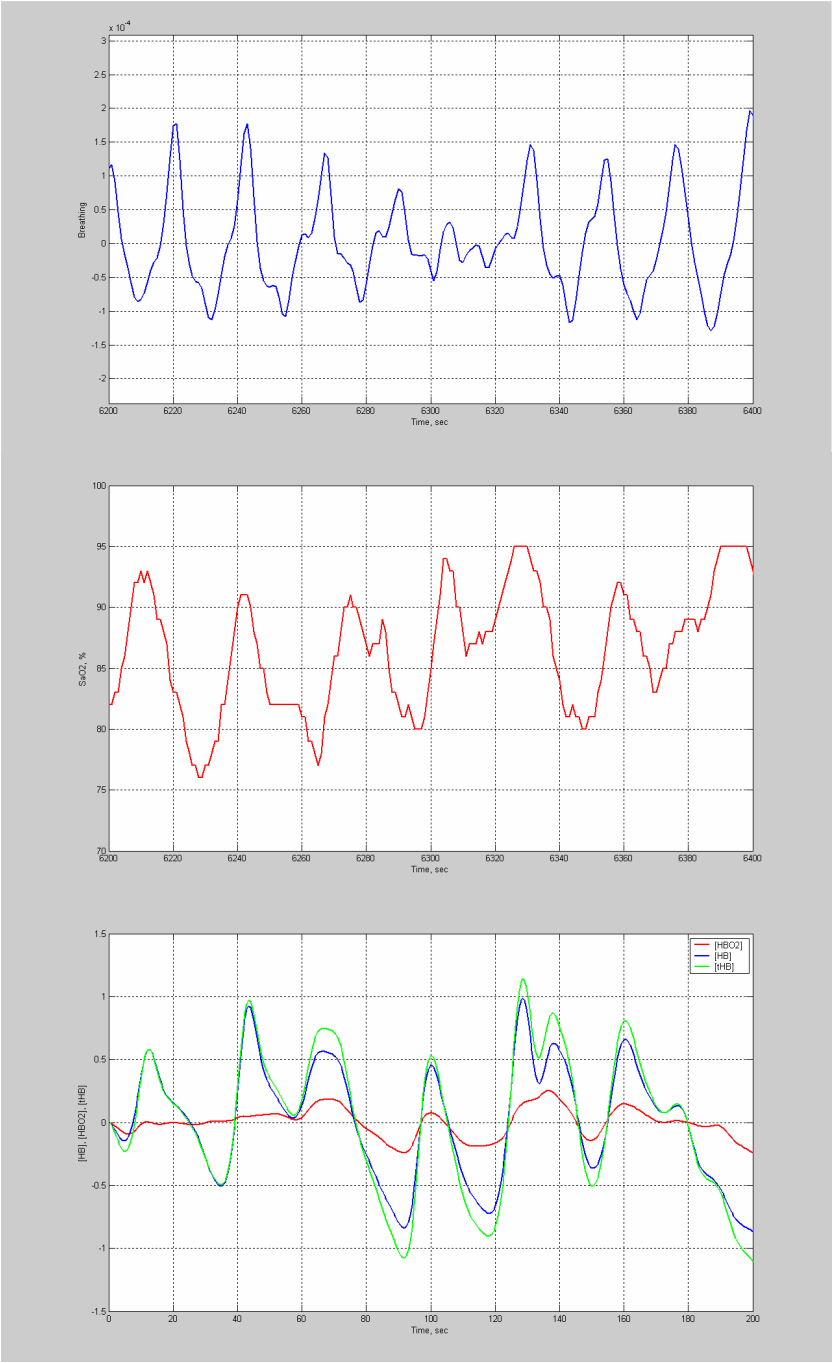


Figure A.5 Synchronized Breathing activity, SaO_2 and cerebral hemodynamics of subject RDN

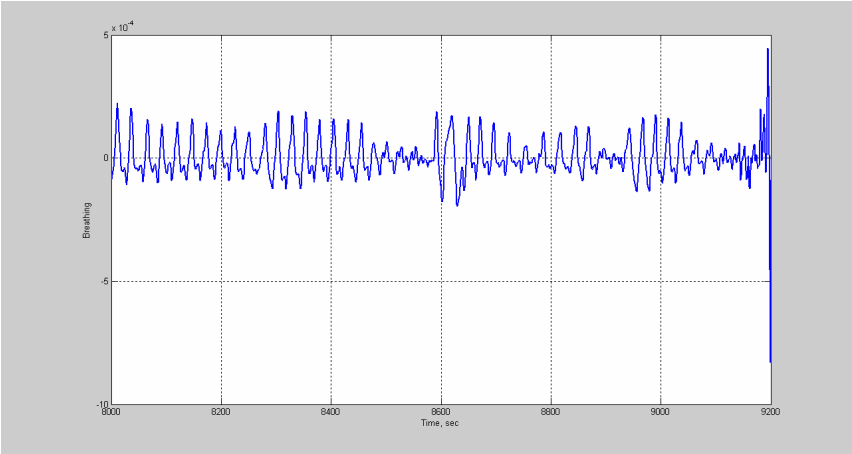


Figure A.6 Breathing activity of subject RDN for 20 mins.

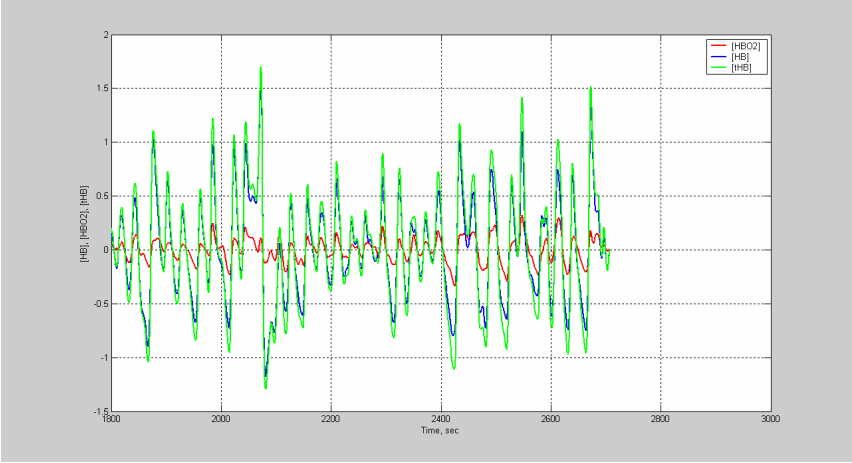


Figure A.7 Cerebral hemodynamics of subject RDN

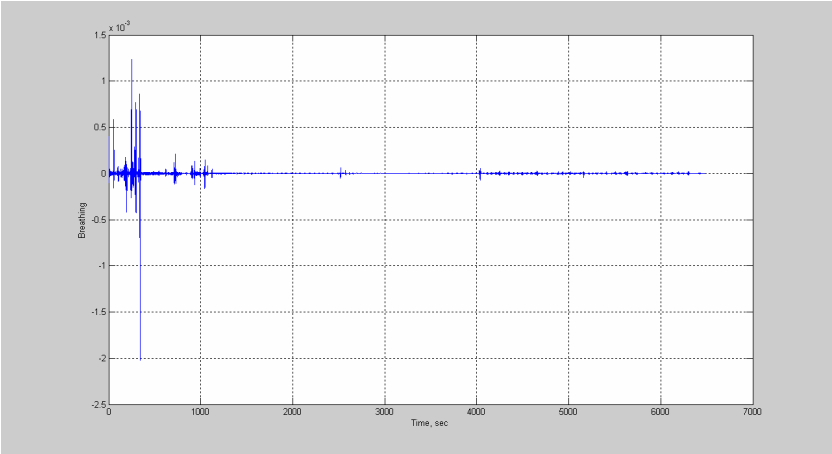


Figure A.8 Breathing activity of subject FA for the whole recording of 116 mins. duration. The high amplitude signals observed around 500 secs are due to motion artifacts

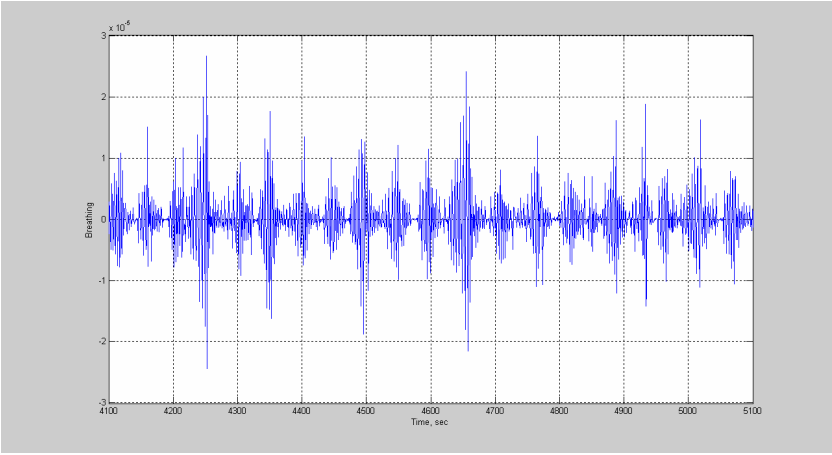


Figure A.9 Breathing activity of subject FA for 1000 secs

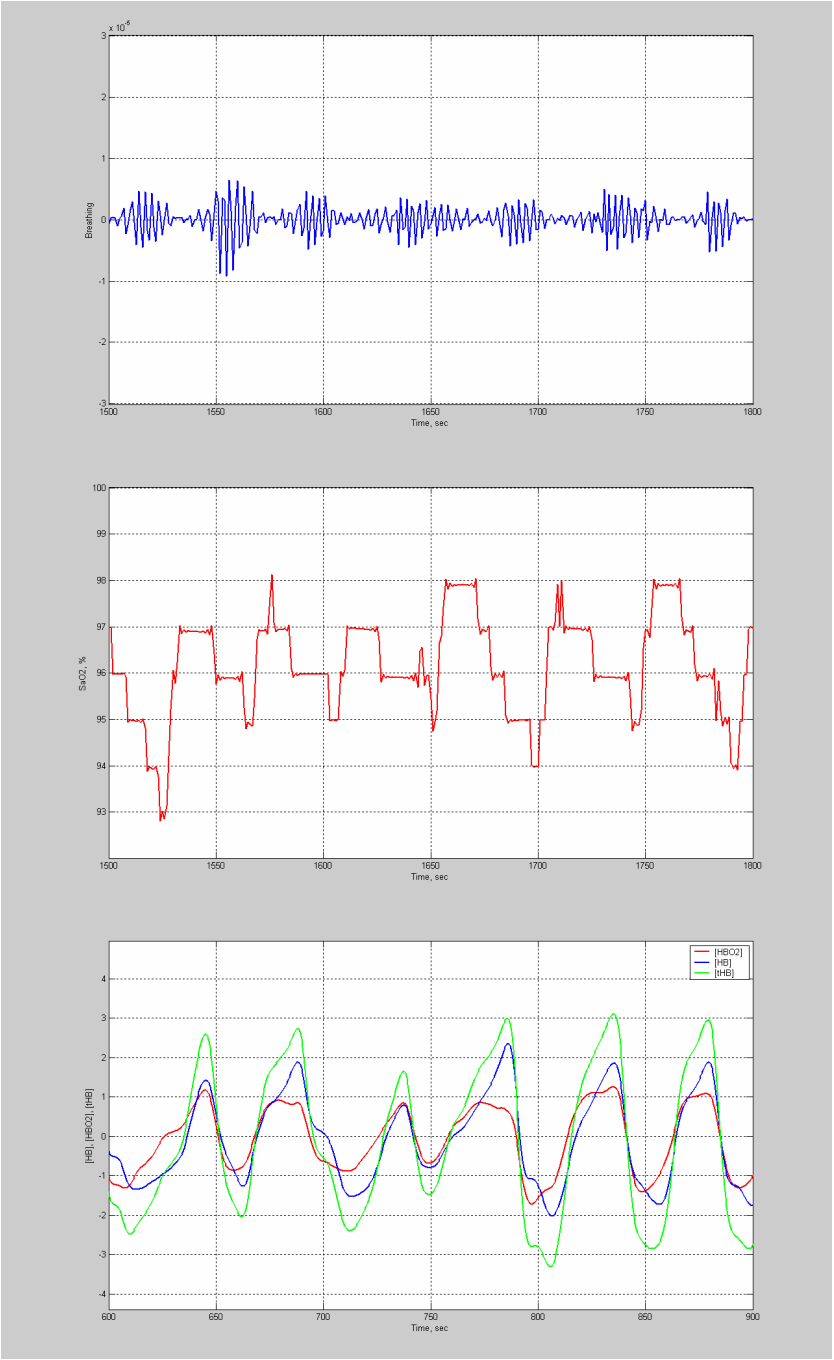


Figure A.10 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject FA

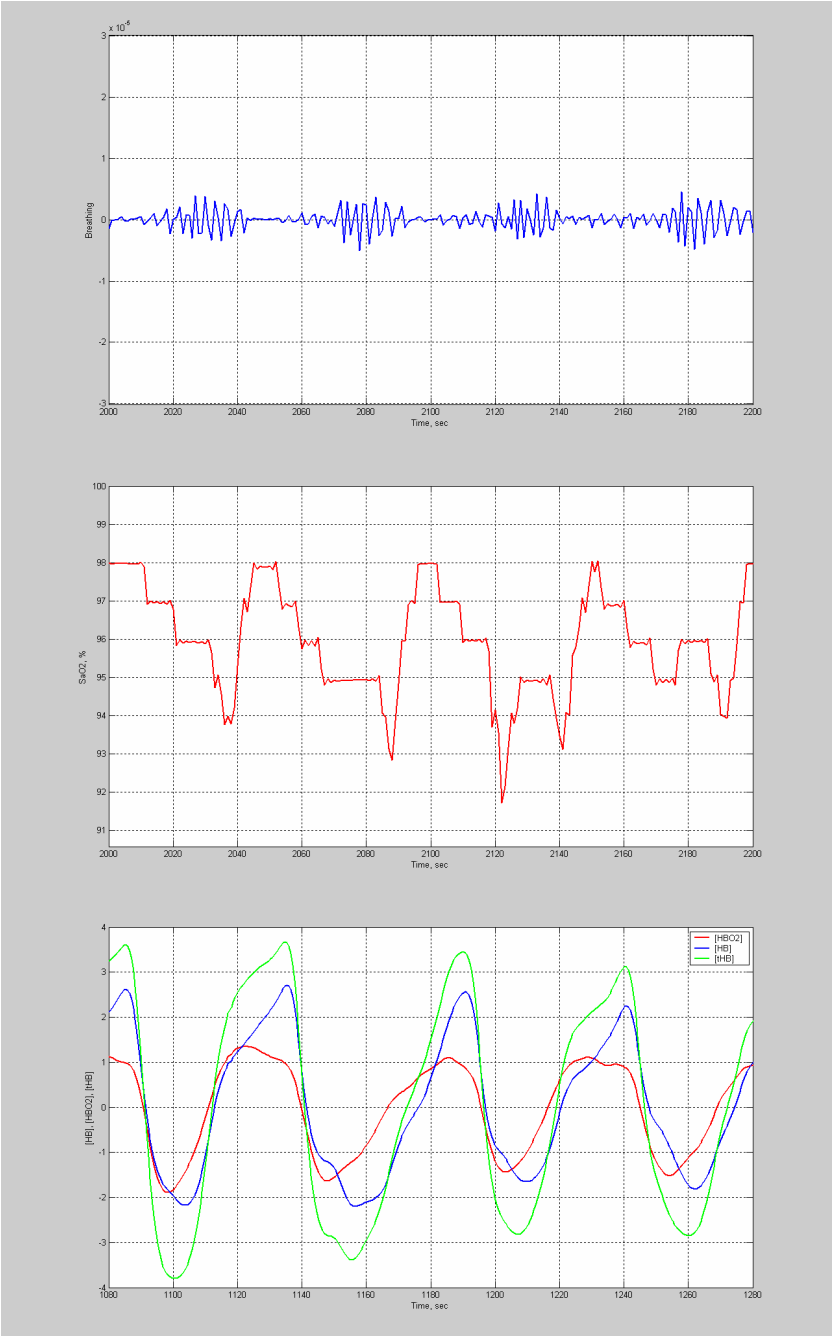


Figure A.11 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject FA

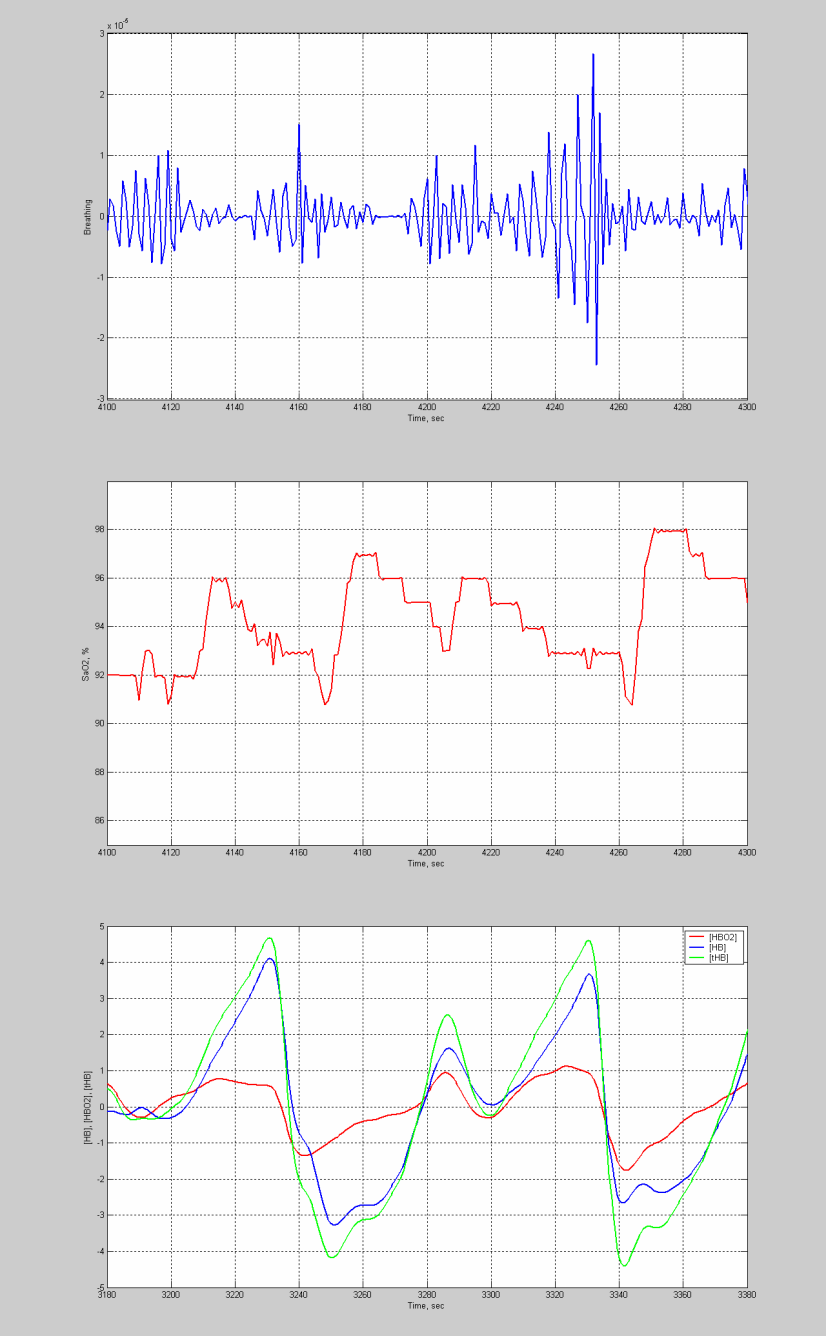


Figure A.12 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject FA

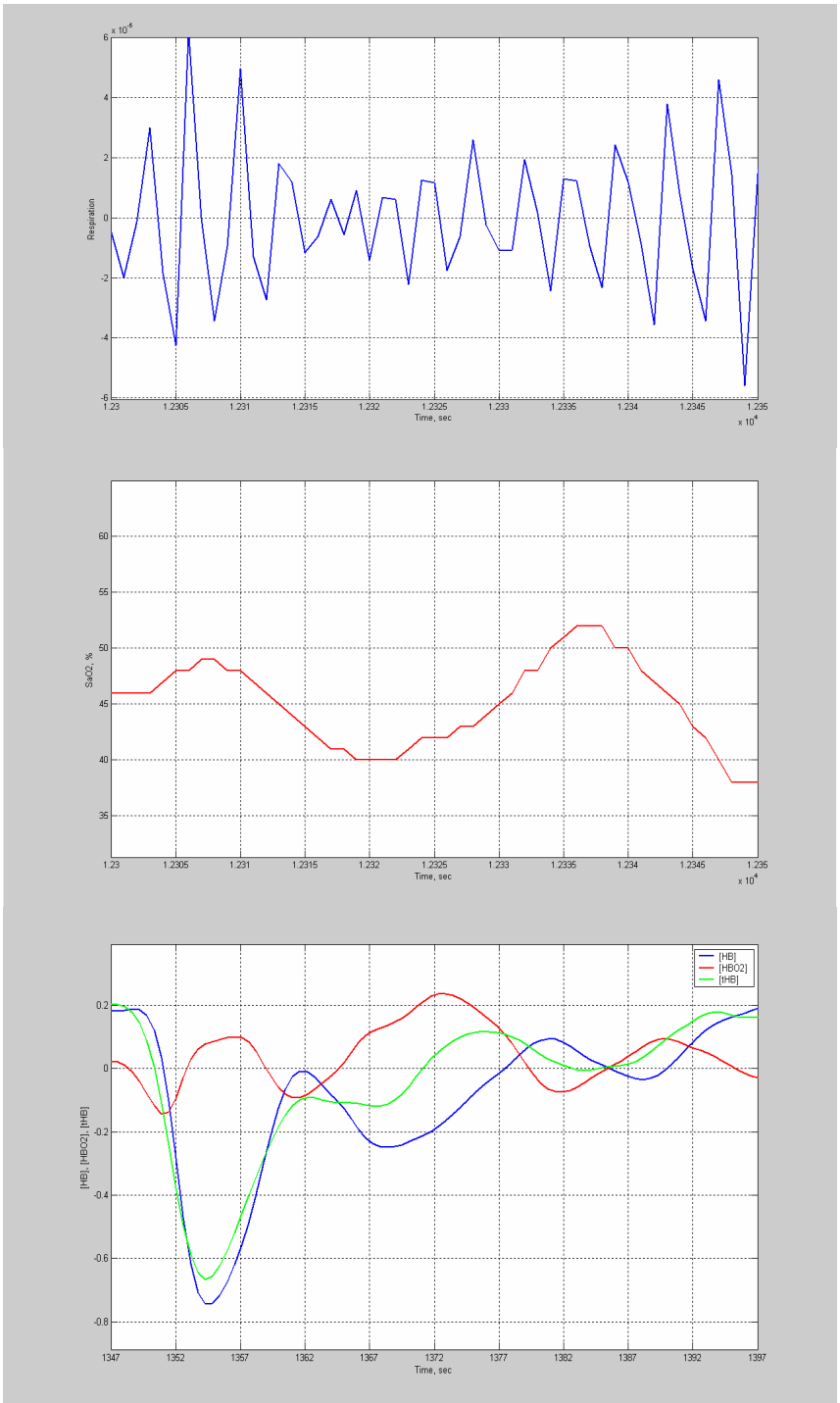


Figure A.13 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject HK

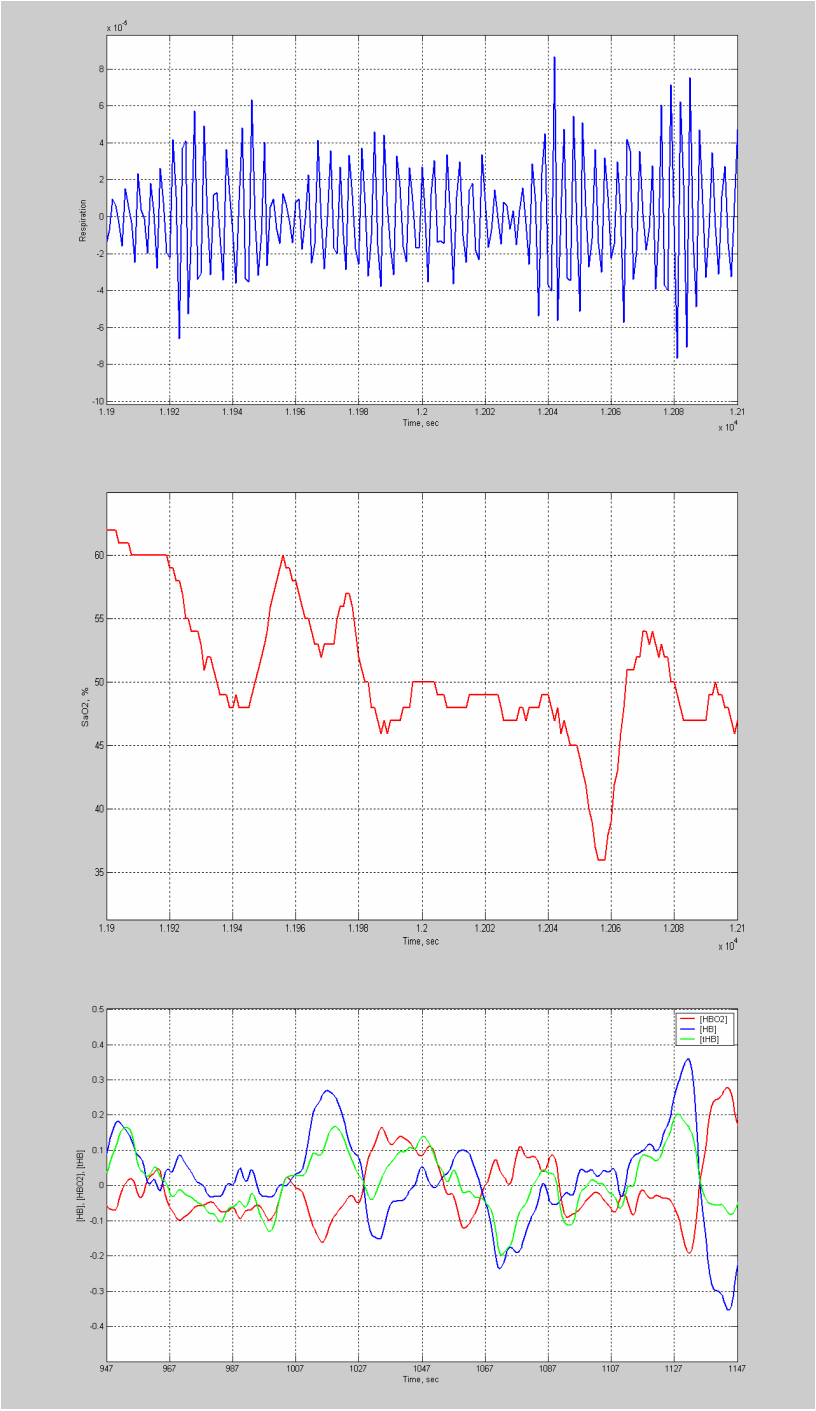


Figure A.14 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject HK

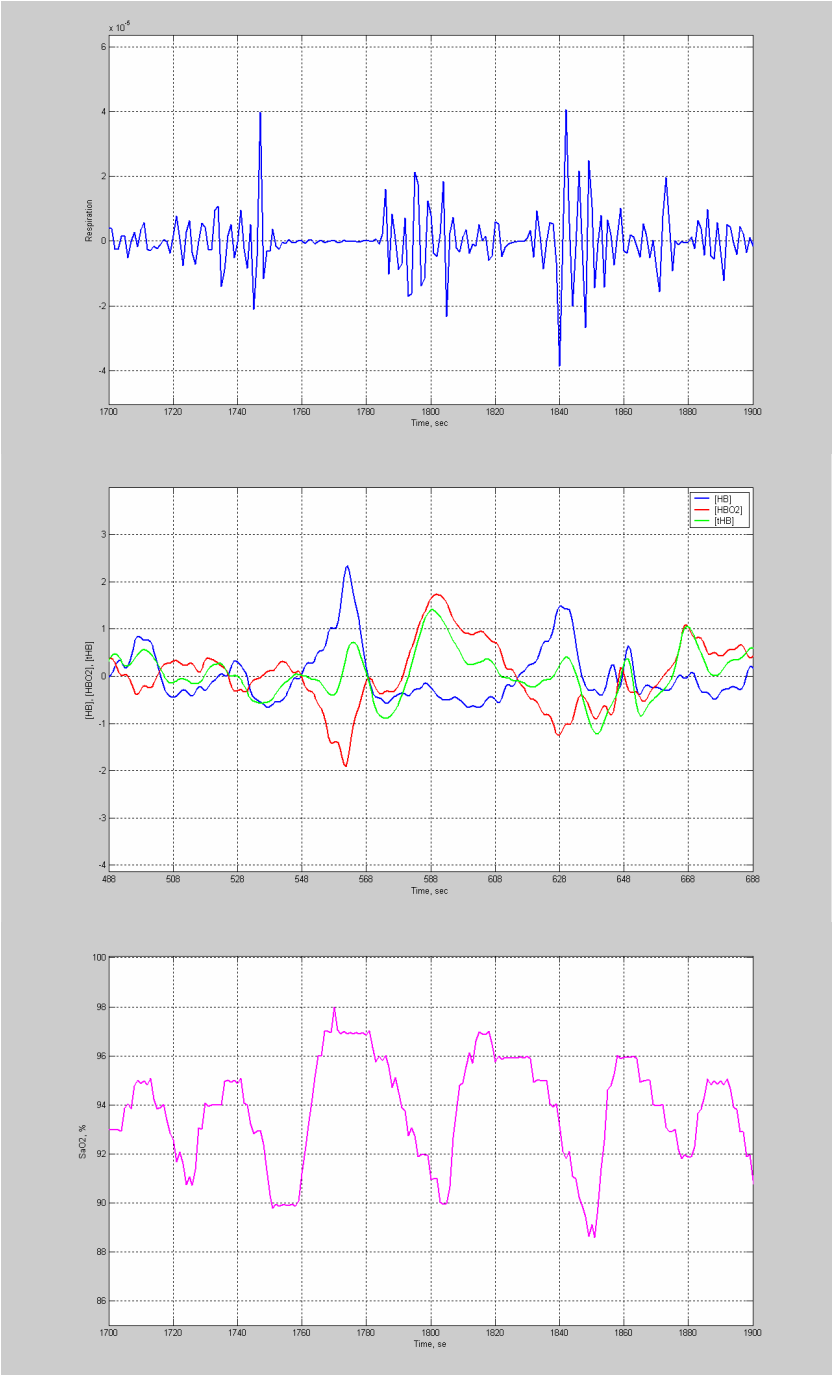


Figure A.15 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject RK

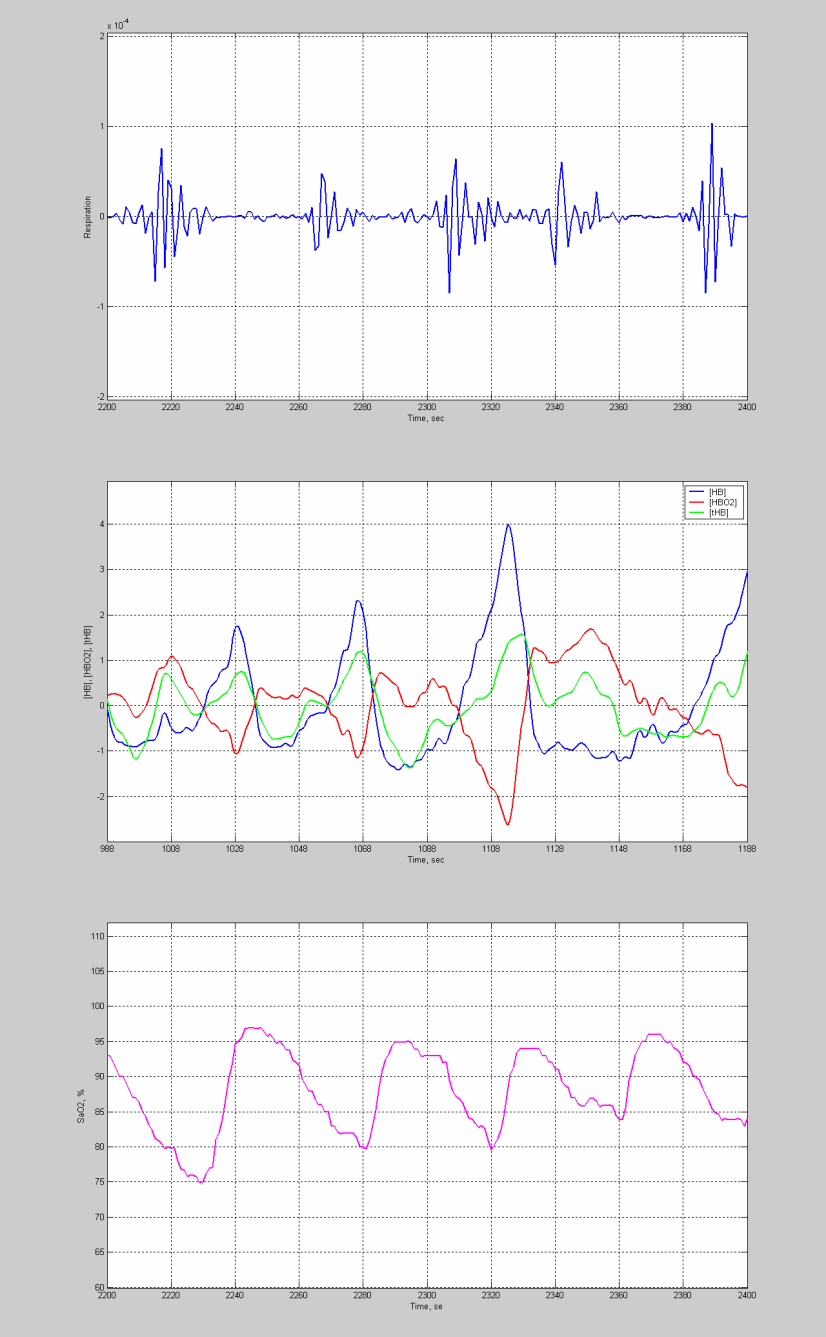


Figure A.16 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject RK

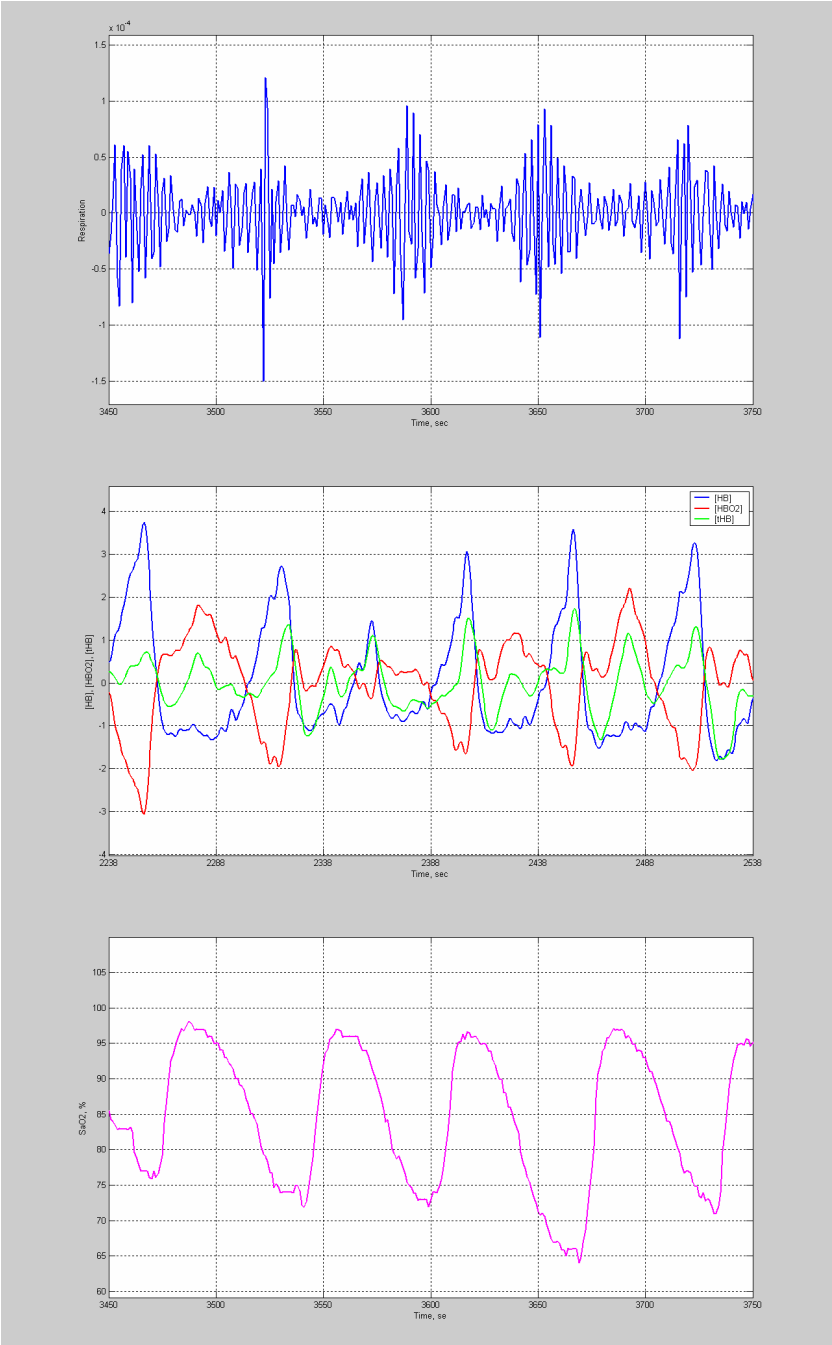


Figure A.17 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject RK

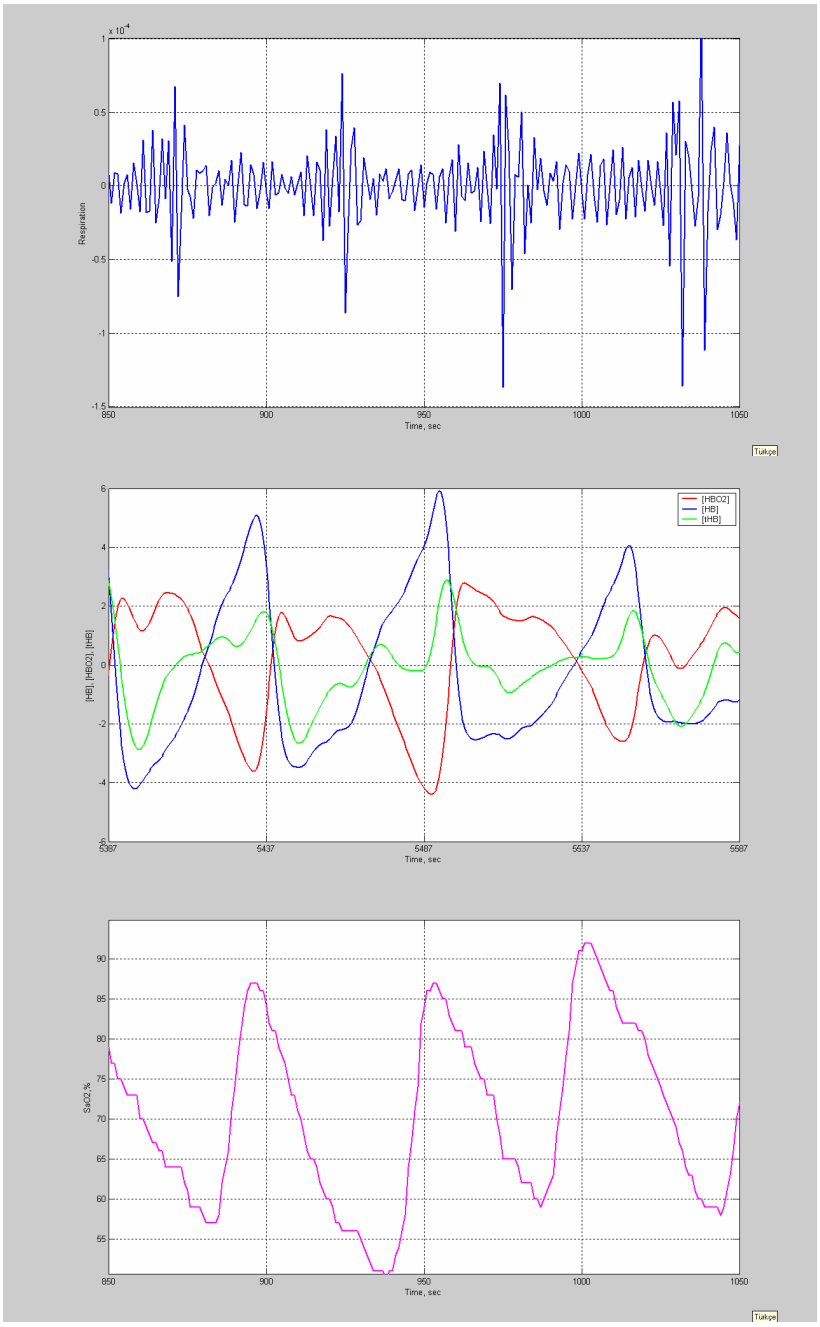


Figure A.18 Synchronized breathing activity, SaO_2 and cerebral hemodynamics of subject RK

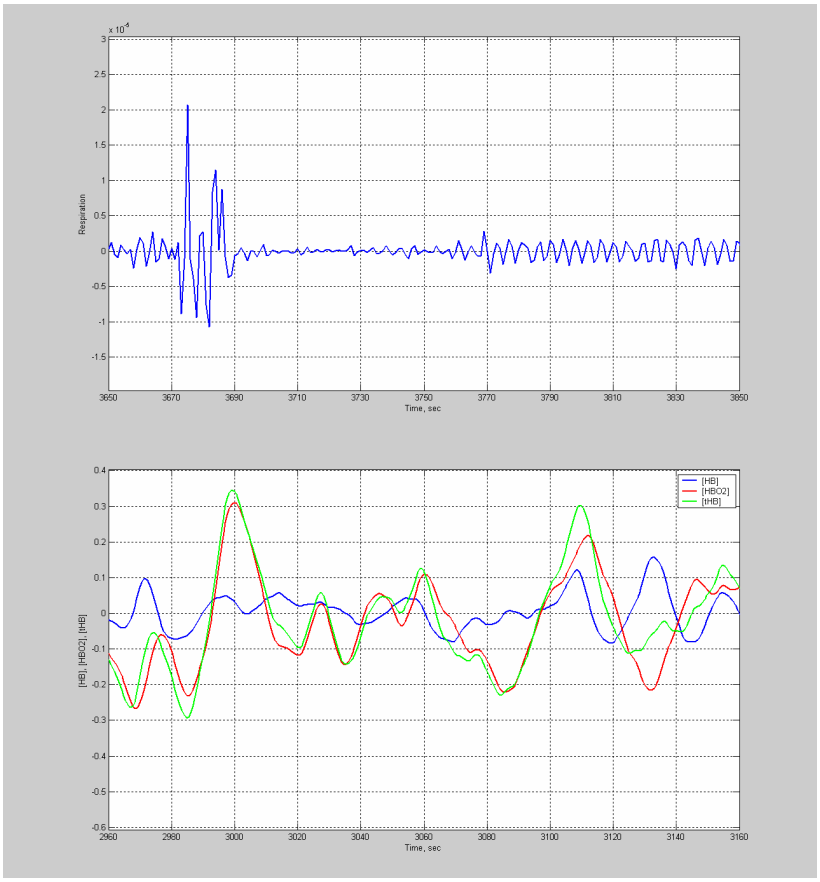


Figure A.19 Synchronized Breathing activity, cerebral hemodynamics of subject MŞ

APPENDIX B. SaO_2 and SO_2 MEASUREMENTS

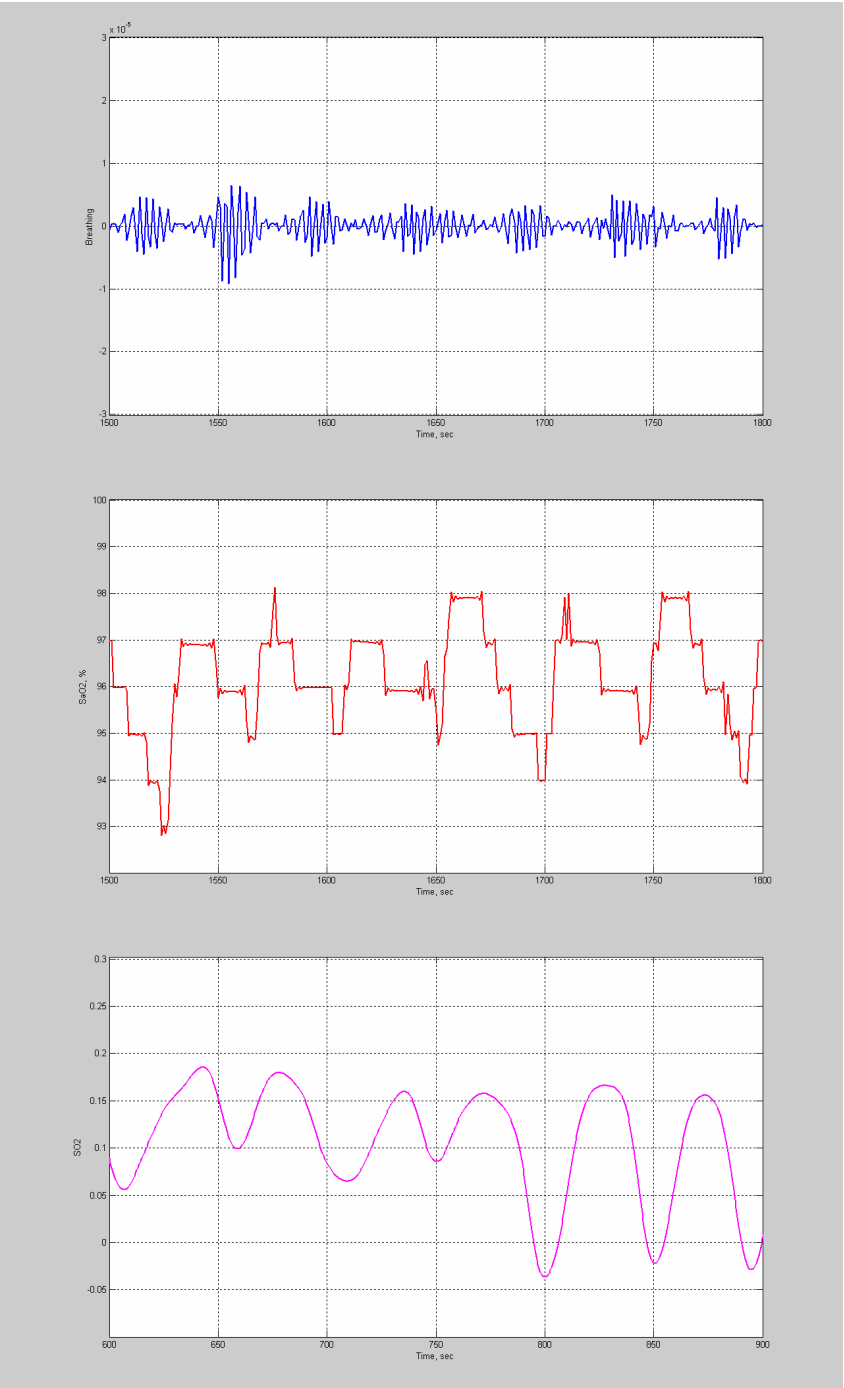


Figure B.1 Synchronized breathing activity, SaO_2 and SO_2 for subject FA

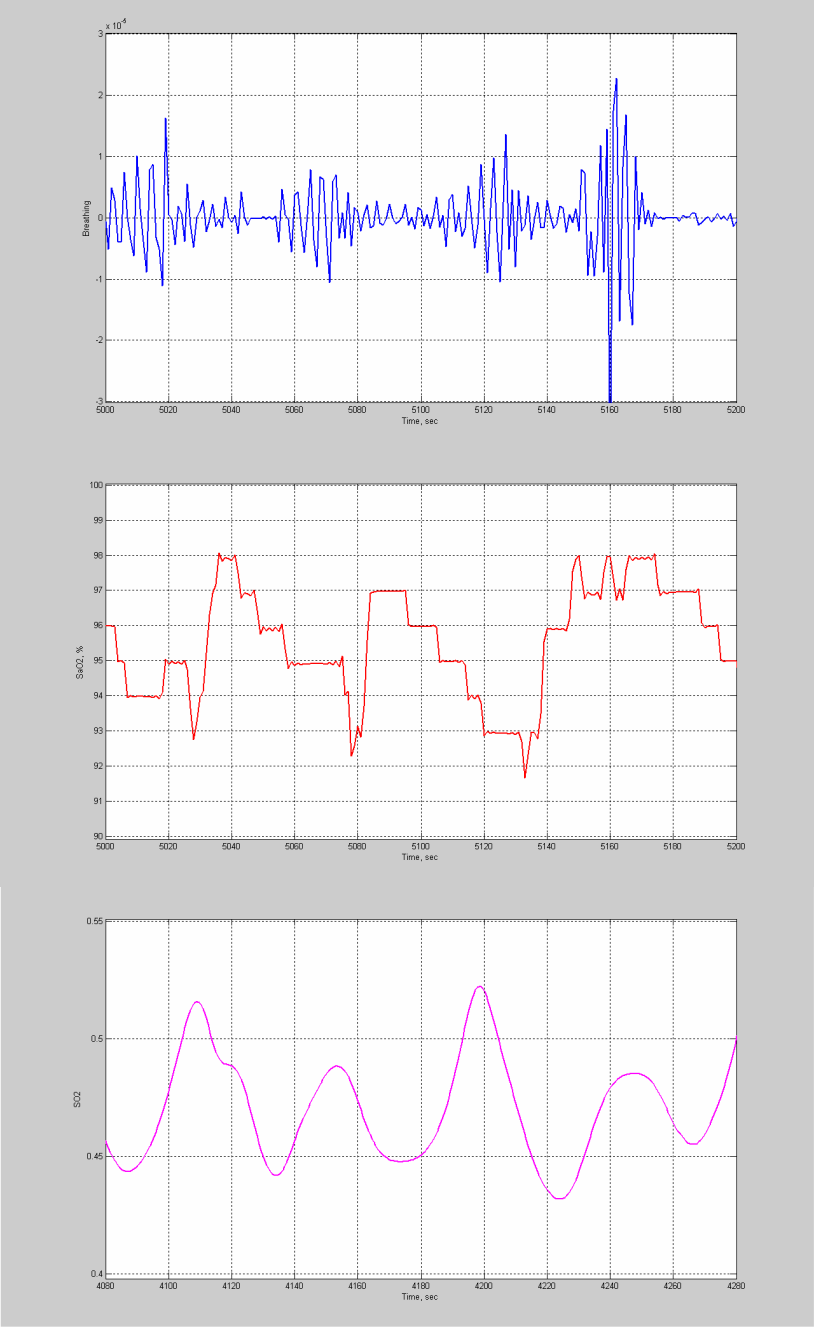


Figure B.2 Synchronized breathing activity, SaO_2 and SO_2 for subject FA

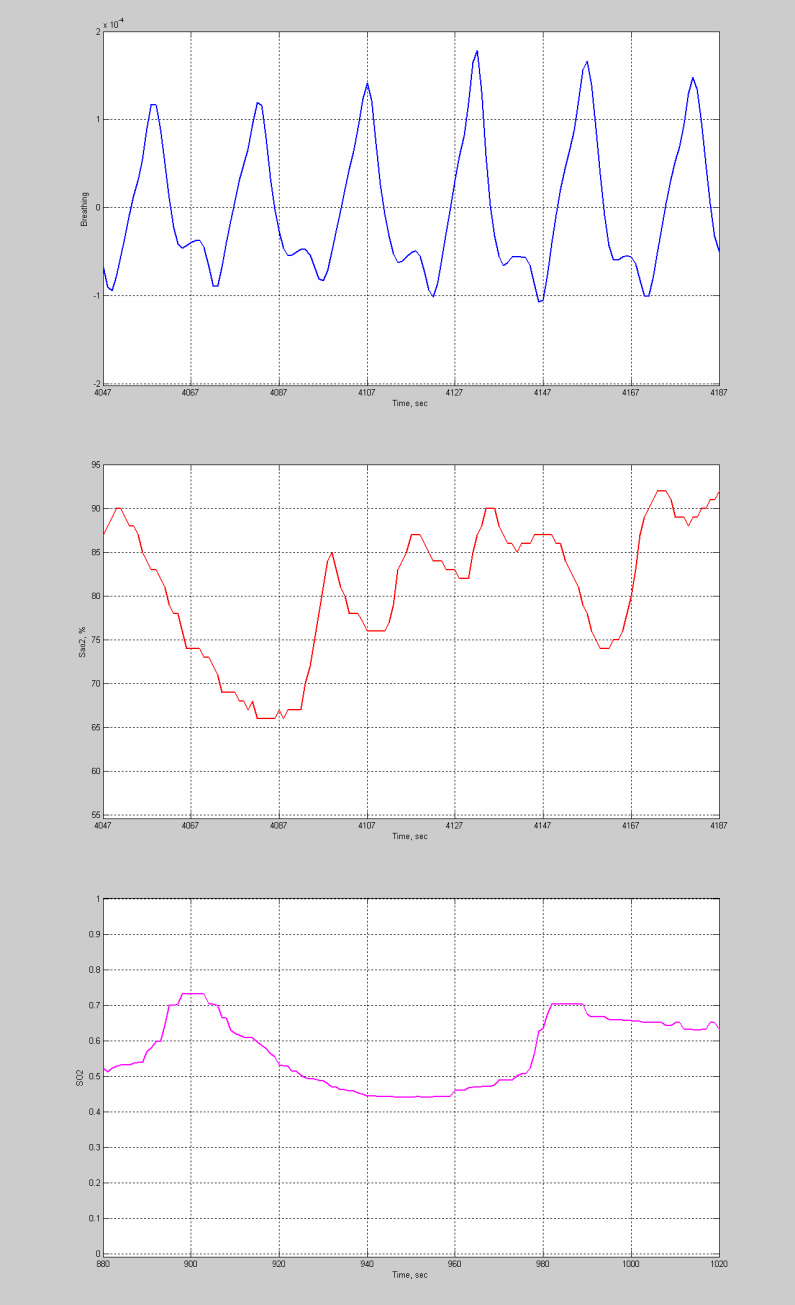


Figure B.3 Synchronized breathing activity, SaO_2 and SO_2 for subject RDN

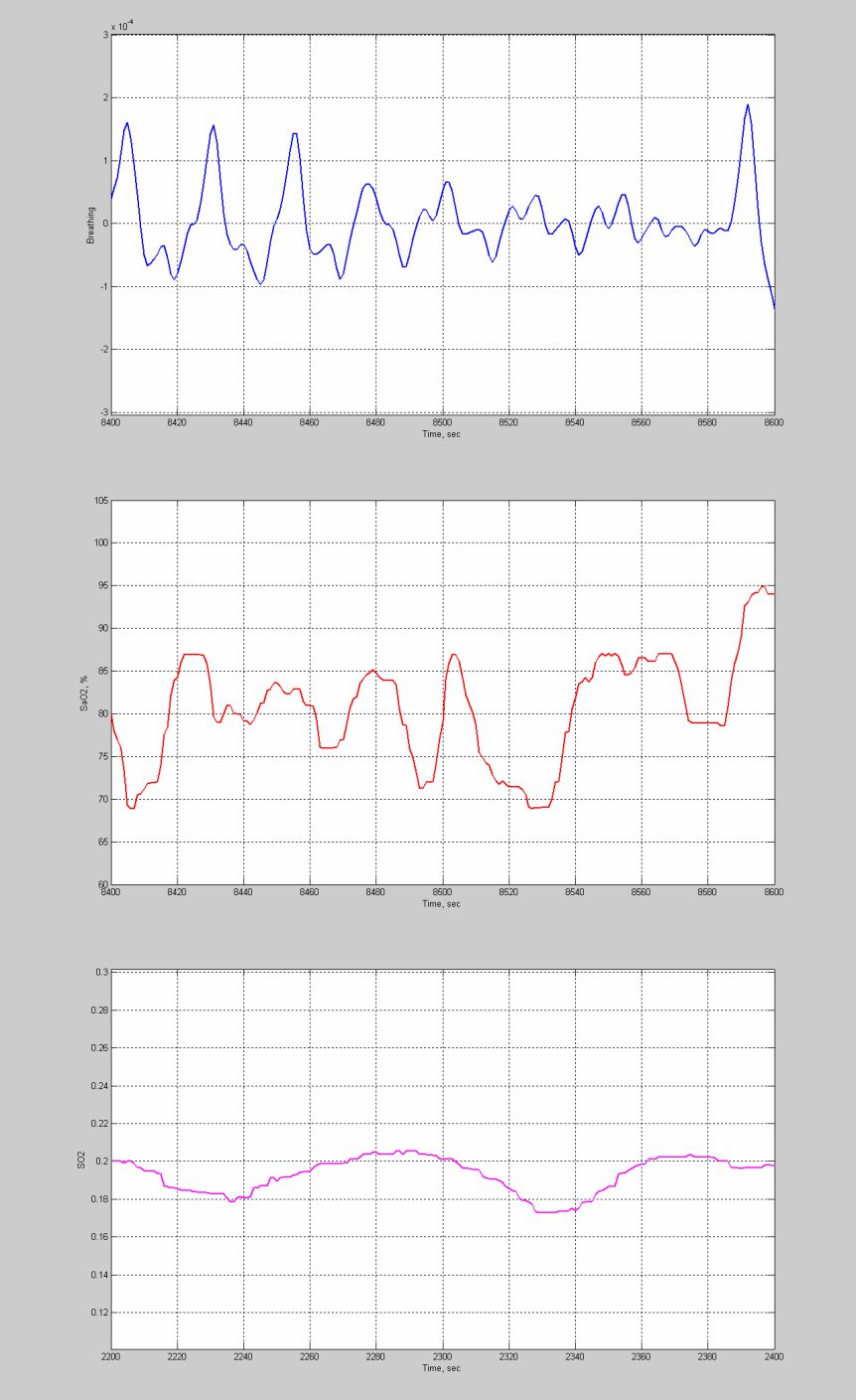


Figure B.4 Synchronized breathing activity, SaO_2 and SO_2 for subject RDN

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