https://ntrs.nasa.gov/search.jsp?R=19970004236 2019-05-13T16:24:50+00:00Z

NASA-CR-203033

IN-52-CR
0531

EFFECTS OF SUSTAINED LOW-LEVEL ELEVATIONS OF CARBON DIOXIDE ON CEREBRAL BLOOD FLOW AND AUTOREGULATION OF THE INTRACEREBRAL ARTERIES IN HUMANS

by

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RUNNING HEAD: **HYPERCAPNIA ON CEREBRAL BLOOD FLOW**

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DEC 11 1996
C.A.S.I.

Abstract:

Cerebral blood flow velocity (CBFv) was measured by insonating the middle cerebral arteries of 4 subjects using a 2 Mhz transcranial Doppler. Ambient CO_2 was elevated to 0.7% for 23 days in the first study and to 1.2% for 23 days in the same subjects in the second study. By non-parametric testing CBFv was elevated significantly by +35% above pre-exposure levels during the first 1-3 days at both exposure levels after which CBFv progressively readjusted to pre-exposure levels. Despite similar CBFv responses, headache was only reported during the initial phase of exposure to 1.2% CO_2. Vascular reactivity to CO_2 assessed by rebreathing showed a similar pattern with the CBFv increases early in the exposures being greater than those elicited later. An increase in metabolic rate of the visual cortex was evoked by having the subjects open and close their eyes during a visual stimulus. Evoked CBFv responses measured in the posterior cerebral artery were also elevated in the first 1-3 days of both studies returning to pre-exposure levels as hypercapnia continued. Cerebral vascular autoregulation assessed by raising head pressure during 10° head-down tilt both during the low-level exposures and during rebreathing was unaltered. There were no changes in the retinal microcirculation during serial

fundoscopy studies. The time-dependent changes in CO_2 vascular reactivity might be due either to retention of bicarbonate in brain extracellular fluid or to progressive increases in ventilation, or both. Cerebral vascular autoregulation appears preserved during chronic exposure to these low levels of ambient CO_2 .

Index terms: microgravity, head-down tilt, evoked blood flow, cerebral arteries, arterial pressure, headache

Introduction:

CO_2 is one of the most potent dilators of cerebral vessels and cerebral resistance vessels are exquisitely sensitive to very minor elevations of arterial CO_2 tension. In contrast to the resistance vessels, the diameter of the major basal cerebral vessels remains constant when arterial PCO_2 is altered (7,11,20). Therefore, changes in cerebral blood flow (CBF, $ml.sec^{-1}$) induced by alterations of arterial PCO_2 can be inferred from changes of cerebral blood flow velocity (CBFv, $cm.sec^{-1}$) measured in the basal arteries. CBFv in the major cerebral vessels can be measured non-invasively using transcranial Doppler (TCD) methodology and the reactivity of the resistance vessels can be estimated. The potent influence of CO_2 on the caliber of cerebral resistance vessels is readily evident with very minor elevations of arterial PCO_2 (14). Hypercapnia is induced routinely in the clinic for the study of intracranial hemodynamics while hypocapnia can be used to treat patients with elevated intracranial pressure.

Autoregulation is well-developed in the cerebral circulation and provides relatively constant blood flow during changes in cerebral perfusion pressure (13,15,22). The proximal M1 segment of the middle cerebral artery (MCA) represents a major basal intracranial artery which maintains a constant diameter allowing for the indirect

estimate of CBF via direct measurements of CBFv using TCD. In addition, the coupling of CBF to local brain metabolism can be estimated in humans via TCD by measuring CBFv responses in the posterior cerebral artery (PCA) during metabolic activation of the visual cortex by visual stimulation (1).

The effects of short-term exposures to hypercapnia on CBF and the changes of brain perfusion during cognitive function in healthy subjects vs patients having cerebrovascular disorders are well-established (15,22). By contrast, little is known about the long-term effects of sustained elevations of CO_2 on either CBF or the ability of the autoregulatory mechanism to protect brain microvessels. In addition, information is lacking as to the effects of sustained exposure to hypercapnia on the interaction of cognitive function with local brain perfusion (8,18). In terms of space flight, it should be emphasized that the effects of microgravity on the above indices of cerebral vascular control are largely unknown. Long-term vasodilation and disruption of autoregulation due to hypercapnia could lead to elevation of microvascular pressure leading to either local or generalized edema with neurological sequelae (17). These effects could be exacerbated by microgravity where it is well-known that a cephalic shift of fluid occurs. In addition to the

potential effects of hypercapnia on crew performance and operations, cerebrovascular responses to sustained low-levels of hypercapnia may have important confounding influences on the outcomes of on-going physiological or human factors studies.

This study was performed to assess the effects of exposure to sustained low-levels of hypercapnia alone, or in combination with simulations of microgravity, on the reactivity of CBF to CO_2 , brain vascular autoregulation, the coupling of CBF to local brain metabolism, and the retinal microcirculation. This data, together with the results derived from the other parallel investigations in the NASA-ESA-DARA Joint CO_2 Study provides information which will be utilized for setting both the nominal level and the upper bound for ambient CO_2 concentrations in the new space station.

Four subjects were studied twice during experimental campaigns lasting 29 days each in the Titan hyperbaric chamber located at the German Aerospace Medical Research Institute in Cologne. The subjects were exposed first to 23 days of 0.7% CO_2 and, during the second campaign, to 1.2% CO_2. TCD technology enabled for the first time the long-term study of cerebral vascular regulation in humans during these conditions.

Methods:

Subjects: The characteristics of the Titan chamber allowed for the maintenance of a fixed level of CO_2 in the atmosphere. In addition, the chamber allowed continuous monitoring of oxygen levels, temperature and humidity while the subjects worked and lived during the two exposure periods of 0.7% and 1.2%, respectively. Four male subjects were studied. They were healthy non-smokers with normal body weights and intermediate levels of physical fitness ranging in age between 22 and 27 years. An inclusion criterion required an adequate transtemporal window for insonation of the middle cerebral artery using TCD. Since the subjects carried out experiments supervised by nine international teams, our times of access to the subjects and measurements were limited to selected days as indicated in **Table 1.**

Cerebral blood flow velocity (CBFv): CBFv was measured using a Multidop X TCD device (DWL, Sipplingen, Germany). Mean CBFv was calculated continuously as the time-average maximum velocity over the cardiac cycle computed from the envelope of the maximum frequencies. In all subjects, the left M1 segment of the middle cerebral artery (MCA) was isonated at a depth of 48 mm. For this MCA segment, neither

arterial pressure nor PCO_2 affects the diameter (7). As emphasized above, changes in CBFv reflect proportional changes in CBF (14,16).

Test protocol: CBFv was measured following a standard protocol which included measurements with the subjects lying in the horizontal position and then with head tilted down by 10° (HDT). HDT was used to simulate microgravity and its associated cephalic fluid shifts for a total period of 19 min. HDT produces prompt elevations in intracranial and cerebral perfusion pressures which are sustained during the stimulus (12,23). In addition, in both the supine and HDT positions, the subjects rebreathed a mixture of 5% CO_2 and 95% O_2 for 2 min periods in order to test the reactivity of the MCA to CO_2. Arterial blood pressure (ABP) was measured continuously during the test protocol using a Finapress 2300^R Blood Pressure Monitor (Ohmeda, Louisville, USA) with the transducer attached to the right index finger. The finger was positioned at head-level to monitor cerebral perfusion pressure. During rebreathing the concentration of CO_2 at the mouth was monitored with all data (CBFv, ABP, CO_2 concentration) displayed continuously.

Visually-evoked dynamic CBFv responses of the posterior cerebral artery (PCA): CBFv was measured also in the PCA in order to study the interaction of CBFv and local brain metabolic rate during mild hypercapnia. CBF is

tightly coupled to regional brain metabolism and function (21). Previous studies of the PCA using TCD have shown rapid responses of CBFv to local changes in brain metabolism (1). For our study, PCA CBFv was monitored to estimate CBF increases secondary to increased metabolic rate of visual cortex. The subjects sat quietly and watched a standard cartoon video while PCA CBFv was monitored. The subjects then closed their eyes for 15 sec and reopened them for 15 sec. This maneuver was repeated 10 times during a particular test and the changes in CBFv (Δ CBFv) while opening vs closing the eyes were expressed as means $\pm$ 1 standard deviation (**Fig 1**)

Fundoscopy: In addition to the ultrasound studies, fundoscopy was performed to assess potential changes in the microcirculation of the retina before and following HDT in hypercapnia. We used a commercial fundoscope (RC 310, Zeiss, Jena, Germany) coupled to a video camera. Mydriasis was induced pharmacologically by Tropicamid^{Rx} and the retinal microcirculation including arteries and veins were examined and vessel diameters determined to assess potential retinal fluid shifts and vascular integrity. The videos were evaluated off-line by an opthamologist.

Blood sampling: In order to estimate arterial acid-base status during the hypercapnia periods, we obtained "arterialized venous blood" from the left hand of the

subjects at several points during each campaign. Vascular dilation was induced by having the subject place the hand in 43° C water for 10 min prior to sampling. This method allows for the withdrawal of nearly arterialized blood via venipuncture with the avoidance of arterial puncture. Estimates of acid-base status are highly accurate with this method in contrast to estimates of arterial oxygenation which are less certain (6). Blood samples were analyzed for pH, PCO_2, HCO_3^- using a Radiometer ABL 330 blood gas analyzer (Copenhagen).

Statistics: In view of the restricted number of subjects we confined our data analysis to use of descriptive statistics (mean and standard deviation) and the non-parametric Wilcoxon signed-ranks test. With this small "n" of four subjects, p values $\leq$ 0.125 were considered statistically significant. Using the Wilcoxon test, significance (*) occurred only when all subjects exhibited the same directional response leading to a minimal significance level accepted at 0.125. Data obtained during the pre-exposure periods served as the control data for the experimental measurements obtained during hypercapnia.

Results:

Central Hemodynamics: Neither level of hypercapnia was observed to elicit systematic or consistent alterations in

either mean arterial blood pressure of heart rate. Therefore, CBFv responses in the intracranial vessels can be taken to reflect primarily responses of cerebral resistance vessels.

Middle Cerebral Artery Studies: Sudden elevation of the inspired CO_2 led to brisk increases in flow velocity and an abrupt return of flow velocity to pre-stimulus levels with the offset of the stimulus.

(1) Mean supine MCA CBFv responses during mild hypercapnia: The mean CBFv (± 1SD) responses in the MCA for all subjects during the two levels of mild hypercapnia are presented in **Fig. 2.** CBFv was elevated in a consistent and statistically significant fashion (p=0.125) in the early days of both hypercapnia periods as compared to the pre-exposure levels of CBFv measured on day (-1) at a CO_2 concentration of 0.03%. The average increase amounted to about 35% above the normocapnic CBFv levels. After the early elevations, CBFv declined progressively over time to return to the pre-exposure levels in both campaigns. CBFv increased relative to the stabilized hypercapnia levels after restoration of eucapnia on day (+1) while the subjects remained in the chamber (1.2%) and also when the subjects were restudied on day 5 after they had been out of the chamber(0.7%). Although we anticipated a greater CBFv response with the higher level of hypercapnia in the second

campaign, we were unable to demonstrate significant differences in CBFv responses between the two levels of hypercapnia. Unfortunately, there were fewer measurement points during the first exposure and the measurement times were not consistent between the two campaigns (Table 1).

(2) Mean supine CBFv MCA responses during CO_2 rebreathing: As expected, the superimposition of an intense hypercapnia stimulus during the period of mild hypercapnia elicited prompt and vigorous increases in CBFv. **Fig 3** shows that the magnitudes of the peak CBFv responses during intense hypercapnia were also greater in the early days of exposure to the mild levels of hypercapnia. These higher peak CBFv values paralleled the higher basal MCA CBFv levels observed during the initial days of the hypercapnic periods (**Fig 2**). The greater peak CBFv responses were a function of the higher basal CBFv levels with the Δ CBFv responses being relatively constant throughout the pre-exposure and exposure periods, i.e. the CBFv increments elicited during rebreathing readjusted as basal CBFv responses readjusted over time.

(4) Mean HDT MCA CBFv values during mild hypercapnia: When HDT was imposed to move fluid cephalad as in microgravity CBFv values were significantly higher early in the periods of mild hypercapnia as is seen in **Fig 4.** However, specific significant increases of CBFv which could

be attributed to the imposition of HDT over and above the CBFv responses secondary to mild hypercapnia were not evident.

(5) Mean HDT MCA CBFv responses during CO_2 rebreathing: HDT was superimposed during rebreathing in an attempt to test the cerebral autoregulatory mechanism by increasing cerebral perfusion pressure in the presence of a stimulus which has the potential to impair autoregulation (17). As expected, the highest values for CBFv were obtained during this maneuver suggesting that, at the highest levels of CO_2 , CBFv may have varied passively with the increased perfusion pressure at least for some of the measurements. As observed with the other measurements, CBFv values during HDT and rebreathing varied as a function of time with the highest values occurring early in the periods of exposure to mild hypercapnia. However, we were unable to demonstrate specific elevations in CBFv due to HDT over and above those elicited by the intense hypercapnia alone. This observation suggests preservation of active resistance vessel responses to elevations in perfusion pressure at these levels of hypercapnia.

(6) Visually-evoked dynamic CBFv responses in the Posterior Cerebral Artery (PCA): In all subjects, the visual stimulus increased CBFv by +30% above baseline CBFv levels. During the early days of exposure to 0.7% CO_2 the

reactivity of CBFv to the visual stimulus appeared to be more pronounced. However, the variability of the responses precluded statistical significance. A similar pattern was observed on day 1 of exposure to 1.2% CO_2 . On day 3, CBFv dropped temporarily and inexplicably but then it increased to follow the trend observed in the first campaign. There was a greater range of CBFv values and more variability in the second campaign.

Fundoscopy: Observations of the retinal vessels before and immediately following the HDT stimulus failed to reveal any significant alterations in either vessel diameters or in the retina itself at any point during either levels of mild hypercapnia.

Acid-base status: For technical reasons, we were unable to obtain reliable blood samples during the first campaign. Acid-base values for the second CO_2 exposure at 1.2% CO_2 are presented in **Fig 5.** "Arterialized" PCO_2 levels were elevated significantly for the first 1-3 days of the exposure after which it was regulated at lower and more variable levels for the remainder of the exposure. The "arterialized" pH generally mirrored the PCO_2 responses over the course of the exposure. Calculated plasma HCO_3^- was elevated significantly for the first 13 days of exposure to CO_2 and then it declined such that it was not different from pre-exposure levels by day 18.

Discussion:

The framework of the DARA-NASA-ESA Joint CO_2 Study provided a unique opportunity to conduct the first long-term non-invasive measurements of cerebral perfusion in humans during periods of sustained exposure to mild hypercapnia. Although several limitations precluded the implementation of a separate timed-control study which would have allowed the specific evaluation of the effects of confinement and variations due to time on cerebral perfusion, we believe that our study provides the following important results:

1) MCA CBFv increased significantly in all subjects in the early days of exposure to both levels of hypercapnia relative to basal CBFv levels in the pre-exposure periods. During both periods of hypercapnia CBFv readjusted over time to return to pre-exposure levels. CBFv did not change from the stabilized hypercapnia levels following restoration of eucapnia.

2) MCA CBFv responses to both levels of hypercapnia were similar in amplitude and pattern. However, complaints of headache were more frequent during the early days of the exposure to 1.2%.

3) MCA CBFv reactivity to CO_2 , as judged by responses during rebreathing, was unchanged from that observed in the pre-exposure period. Higher peak CBFv responses in the

early days of mild hypercapnia simply reflected higher basal CBFv responses with Δ CBFv responses during intense hypercapnia being similar to those in normocapnia.

4) The superimposition of HDT to elevate cerebral perfusion pressure during either period of mild hypercapnia and during rebreathing did not alter MCA CBFv responses in a consistent fashion. This implies that the cerebral autoregulatory mechanism is preserved during these levels of sustained hypercapnia and periods of intense hypercapnia.

5) The increments of CBFv evoked in the PCA by visual stimulation tended to be greater in the early days of exposure to mild hypercapnia. Although these responses were more variable than the MCA responses, the results suggests that the regional CBF response to a standard increase in local brain metabolic rate may be greater early after exposure to mild hypercapnia.

6) The various stresses of mild vs intense hypercapnia and HDT failed to elicit consistent morphological changes in either the retinal vessels or the retina itself.

7) Analysis of "arterialized" venous blood during the higher level of mild hypercapnia indicated that estimated arterial PCO_2 was elevated significantly during the early days of exposure with subsequent readjustment of PCO_2 toward lower, but still elevated levels as the hypercapnia

continued. Arterial pH appeared to mirror the PCO_2 responses whereas plasma HCO_3^- was elevated early in the exposure declining later.

MCA CBFv responses: The assumption that diameters of the basal cerebral arteries, their flow profiles, and the angles between the ultrasonic beam and the course of the vessel remain constant has been demonstrated to be valid, particularly under conditions of hypercapnia vs hypocapnia (7). Therefore, percent changes in the volume rate of cerebral blood flow are equal to percent changes in velocity of flow in the basal arteries. The acute cerebral vasodilating effects of hypercapnia and the vasoconstriction effects of hypocapnia have been demonstrated repeatedly by various methods including direct observation of pial vessels through transcranial windows (5), angiographically (11) and using radiolabelled microspheres (25). Although the cerebral vasodilator response to hypercapnia has been shown to be dependent upon the level of arterial pressure, especially when arterial pressure drops below 70 mmHg (2,9,24), the mean arterial pressure was not observed to be altered significantly by various levels of hypercapnia or HDT in our study. Hence, the CBFv responses we observed primarily reflect responses of the cerebral resistance vessels.

This study represents the first analysis of CBF responses to chronic exposures to mild hypercapnia in humans. The response patterns for CBF in humans are qualitatively similar but lower in amplitude than the actual CBF responses measured by radiolabelled microspheres in conscious sheep exposed to 5% CO_2 for several days (25). Hence the new finding of a time-dependent readjustment of CBF during continued hypercapnia in humans confirms the earlier animal data. In the sheep study it was demonstrated also that CBF was higher during the initial period of exposure to CO_2 with a subsequent readjustment of CBF to stabilize at a lower level as the hypercapnia continued. Yang and Krasney (25) also reported a significant sustained elevation of cerebral metabolic rate of oxygen in the sheep during hypercapnia. It is unclear whether the mild levels of hypercapnia we elicited in our subjects would have resulted in similar increase in brain metabolic rate.

In view of the sensitivity of the cerebral vasculature to CO_2, we anticipated that CBFv levels would be higher during 1.2% CO_2 exposure than during 0.7% CO_2 exposure particularly since TCD has been shown to detect such differences acutely. Several factors may have contributed to our inability to detect significant differences between the two levels: We made fewer measurements in the first campaign compared to the second, ventilatory responses of

the subjects may have differed between the two campaigns, unfortunately, PCO_2 data from the first campaign is lacking, and thirdly, the small number of subjects may have contributed to the variability.

What is the mechanism for the return of CBF levels toward pre-exposure values as the hypercapnia stimulus continues in man and in animals? It is well established that the primary stimulus for relaxation of brain resistance vessels during hypercapnia is increased $[H^+]$ in brain extracellular fluid (13). Plasma $[HCO_3^-]$ is retained in both humans (**Fig 5**) and in sheep during hypercapnia (25); this probably serves to lessen the severity of the respiratory acidosis. On the other hand, the classic hypothesis of Severinghaus et al (19) implies that brain extracellular fluid (ECF) $[HCO_3^-]$ is adjusted to regulate brain ECF $[H^+]$ during chronic hypocapnia or hypercapnia (3,4). Thus brain ECF $[HCO_3^-]$ could increase over time and reduce the vasodilator $[H^+]$ stimulus. This mechanism probably played a prominent role in readjusting CBF in the sheep study where the arterial PCO_2 was "clamped" at a constant level (25). By contrast, the arterial PCO_2 was allowed to vary during both hypercapnia exposures in the present study. In this regard, the arterial PCO_2 was elevated by much as 6 torr during the first 3 days of the study after which it declined to somewhat lower levels (**Fig**

5). The later decline in PCO_2 was very likely mediated by a time-dependent increase in ventilation. The parallel study by Hoffmann et al (10) found elevations in ventilation both at rest and during exercise which became significant on day 5 following induction of hypercapnia. A comparison of the initial basal and rebreathing CBFv responses during the 1.2% CO_2 exposure in **Figs 2 and 3** with the PCO_2 time course in **Fig 5** reveals that the CBFv responses are well-correlated with the arterial PCO_2 response pattern. Therefore, while retention of $[HCO_3^-]$ in brain ECF may have contributed to the later declines of CBFv, it seems more likely that the readjustment of CBFv observed in the present study can be attributed to a decline of arterial PCO_2 secondary to a time-dependent increase in ventilation.

Since CBFv had readjusted to a lower level as hypercapnia continued, one might have expected CBFv to decline when the hypercapnia was discontinued. Instead, CBFv increased at days (+1) and (+5) (**Fig 2**) while the estimated PCO_2 was variable (**Fig 5**) and ventilation and end-tidal CO_2 fell (10). It is difficult to account for this lack of predicted response particularly since retention of $[HCO_3^-]$ in brain ECF should have rendered the cerebral vessels more responsive to a decline in PCO_2. Perhaps other non-specific factors such as anticipation of the study termination and exit from the chamber played a

role in maintaining the CBFv at levels higher than expected. CBF remained elevated after termination of hypercapnia in the sheep study as well primarily due to continued elevation of brain metabolic rate (25).

Visually-evoked PCA CBFv responses: To our knowledge, this study represents the first investigation of visually-evoked flow responses in humans during sustained hypercapnia. Although the data were variable, the results suggest that the regional-evoked flow responses to a standard visual stimulus may be enhanced during the early period of exposure to both levels of hypercapnia. This could reflect an increased CBFv response due to the elevated $[H^+]$ vasodilator stimulus adding to the vasodilator metabolic products being released locally by the visual cortex. Alternatively, the visual cortical metabolic response to the standard visual stimulus could have been enhanced in the presence of hypercapnia which in turn would lead to augmented metabolic vasodilation.

In summary, our data indicate a readjustment of cerebral blood flow over time during exposure to low-levels of hypercapnia. This is most likely secondary to a time-dependent increase in ventilation. Despite the modulation of the flow responses, the ability of brain autoregulatory response to protect the brain and ocular microcirculations seems to be preserved at these levels of hypercapnia.

Significant and morphological alterations of the retina or the retinal vessels could not be detected with our method. There is suggestive evidence for an effect of hypercapnia on coupling between regional metabolism and flow. Although there was greater incidence of headache reported in the initial phases of exposure to the higher level of hypercapnia, this was not correlated with discernible differences in cerebral perfusion patterns. More specific studies are required to answer the questions raised by this exploratory investigation. Thus, sustained exposures to mild hypercapnia elicit significant adjustments in the cerebral circulation. However, the cerebral vascular autoregulatory mechanism appears preserved at chronic hypercapnia levels up to 1.2% CO_2 as well as during brief periods of intense hypercapnia.

Acknowledgments: The authors wish to acknowledge the outstanding support for our study provided by the technical and scientific staff at the *Deutsche Gesellschaft fuer Luft- Raumfahrt* (DLR) in *Koeln,* Germany without which this study could not have been accomplished. We are also grateful for the enthusiastic participation and cooperation of our experimental subjects. This study was supported by grant 95-CO2-O2D from NASA and DARA. As further, we thank Klaus Willmes v. Hinckeldey, Ph.D. for statistical support.

Legend for Table:

Table 1: Times for cerebral blood flow velocity, fundoscopy and blood sampling are indicated for both experimental campaigns. Variation in sampling times occurred primarily in the early days of both campaigns.

Legends for Figures:

Figure 1: Visually - evoked cerebral blood flow velocity responses in the posterior cerebral artery obtained from one test run in a subject. The mean values of ten responses with the variability envelope are plotted.

Figure 2: Mean cerebral blood flow velocity responses for all four subjects in the supine position obtained at various time points in both campaigns.

Figure 3: Mean cerebral blood flow velocity responses for all four subjects in the supine position during rebreathing obtained at various time points in both campaigns.

Figure 4: Mean cerebral blood flow velocity responses for all four subjects in the head-down tilt position while rebreathing obtained at various time points in both campaigns.

Figure 5: Mean acid-base values for all four subjects estimated from "arterialized" venous blood samples obtained at various time points during exposure to 1.2% CO_2 .

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Tab 1: Timetable

CO2-Study 0.7%

Days	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	+1	+2	+3	+4	+5
TCD-MCA	x	x						x						x					x						x				x
TCD-PCA		x	x					x						x					x						x				x
Funduscopy	x	x						x						x					x						x				x
Blood Sampling	x																		x						x				x

CO2-Study 1.2%

Days	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	+1	+2	+3	+4	+5
TCD-MCA	x	x		x				x						x					x		x				x				x
TCD-PCA	x	x		x				x						x					x		x				x				x
Funduscopy	x	x		x				x						x					x		x				x				x
Blood Sampling	x	x		x				x						x					x						x				x

TCD = Transcranial Doppler Sonography
MCA = Middle Cerebral Artery
PCA = Posterior Cerebral Artery

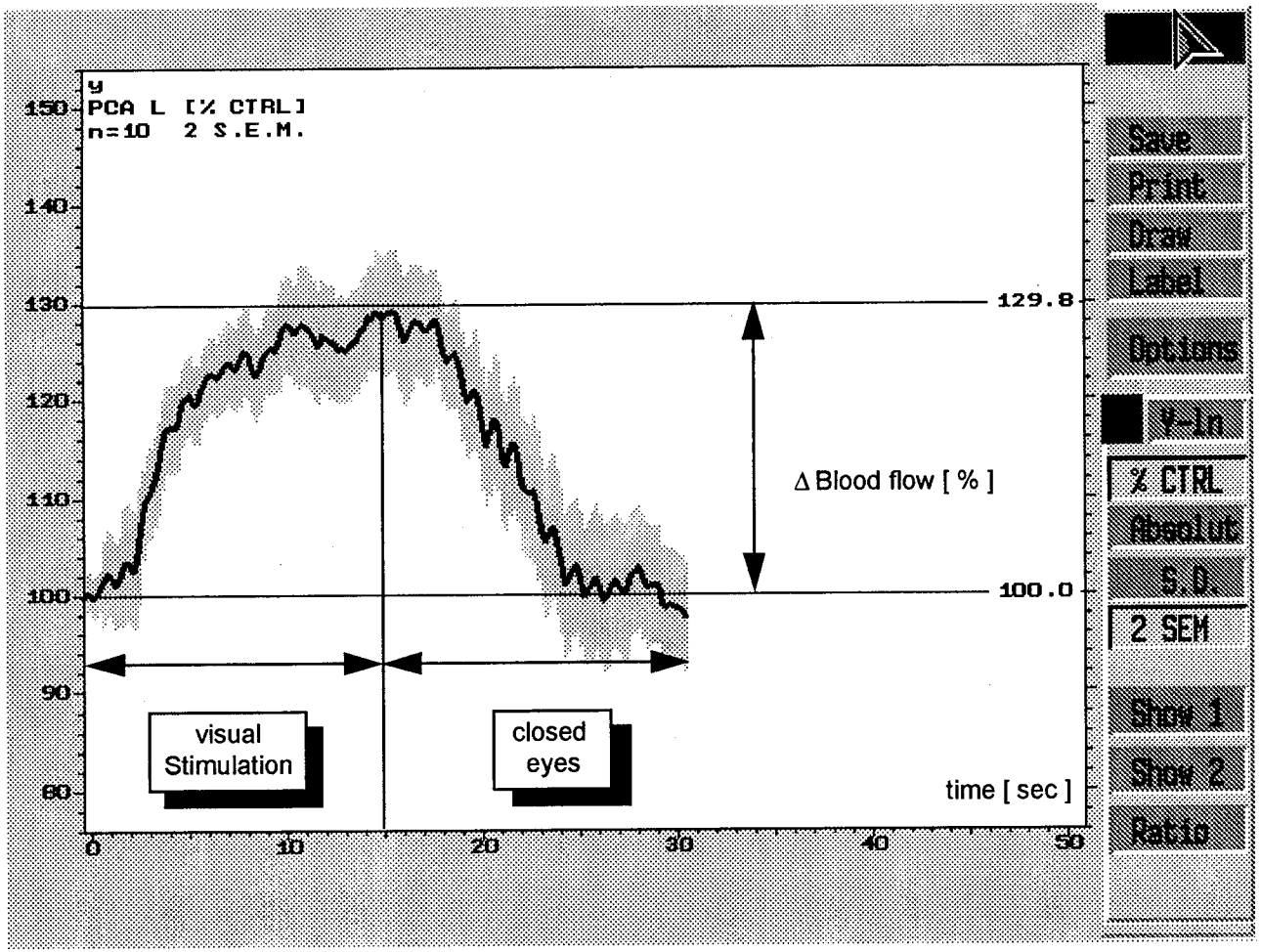


Fig 1: PCA-Stimulation; Curve showing plot of 10 averaged cycles

Fig 2

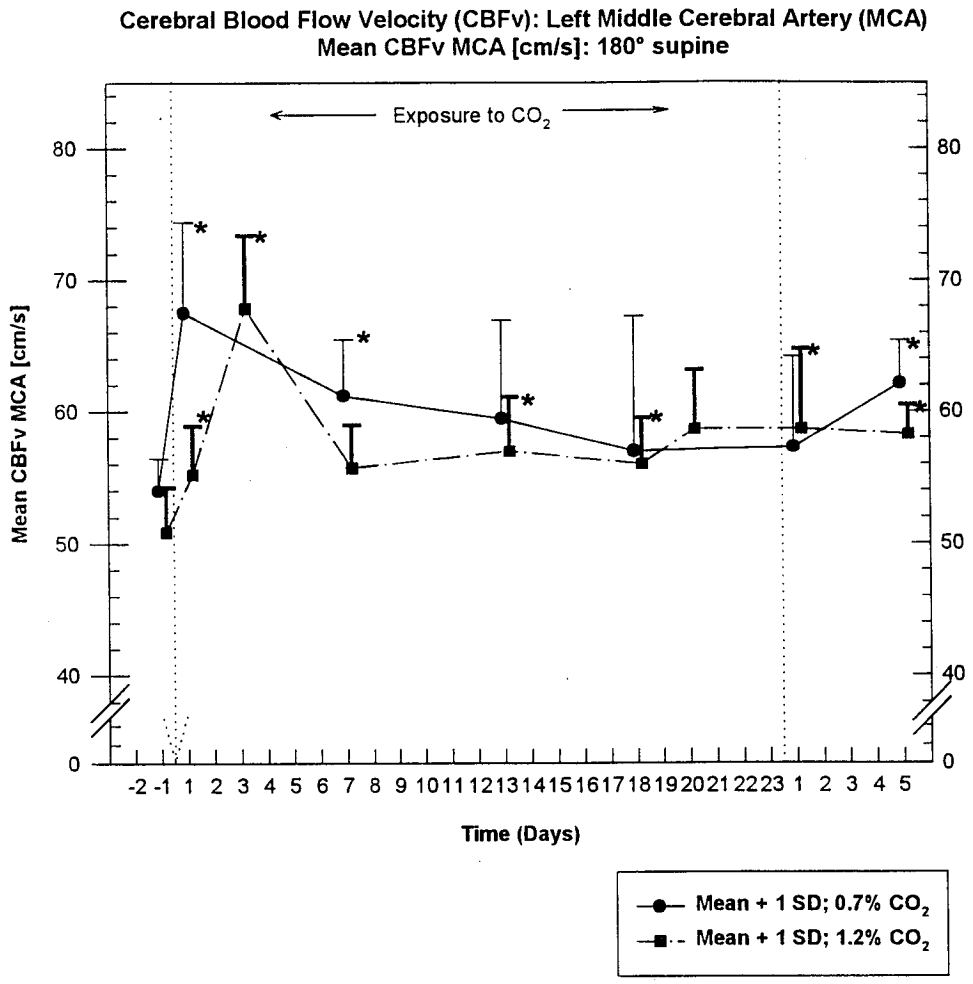

Cerebral Blood Flow Velocity (CBFv): Left Middle Cerebral Artery (MCA)
Mean CBFv MCA [cm/s]: 180° supine
Exposure to CO_2
Mean CBFv MCA [cm/s]
80
70
60
50
40
0
-2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 1 2 3 4 5
Time (Days)
Mean + 1 SD; 0.7% CO_2
Mean + 1 SD; 1.2% CO_2

Fig 3

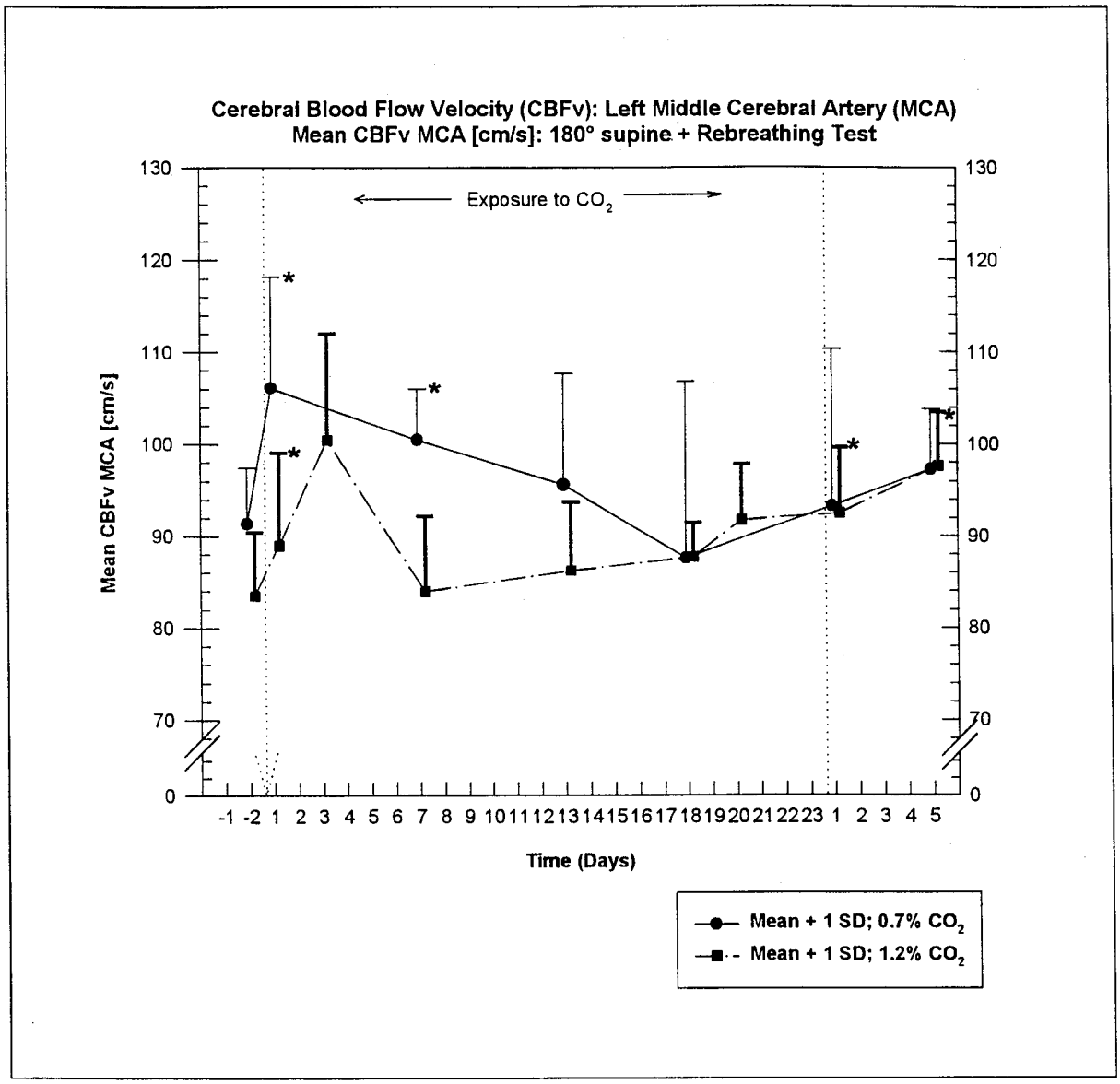

Cerebral Blood Flow Velocity (CBFv): Left Middle Cerebral Artery (MCA)
Mean CBFv MCA [cm/s]: 180° supine + Rebreathing Test
Exposure to CO_2
Mean CBFv MCA [cm/s]
130
120
110
100
90
80
70
0
-1 -2 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 1 2 3 4 5
Time (Days)
Mean + 1 SD; 0.7% CO_2
Mean + 1 SD; 1.2% CO_2

Fig 4

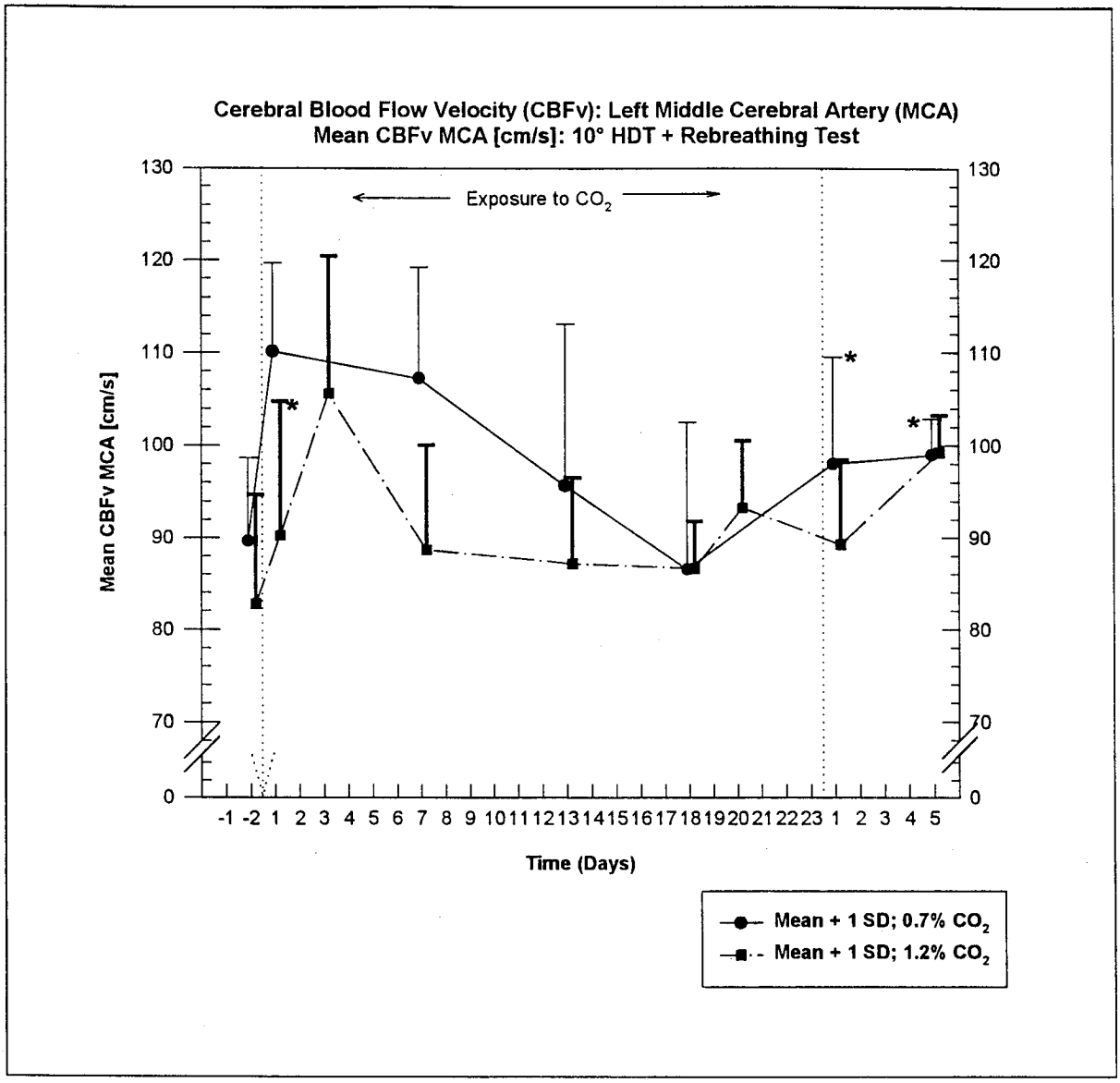
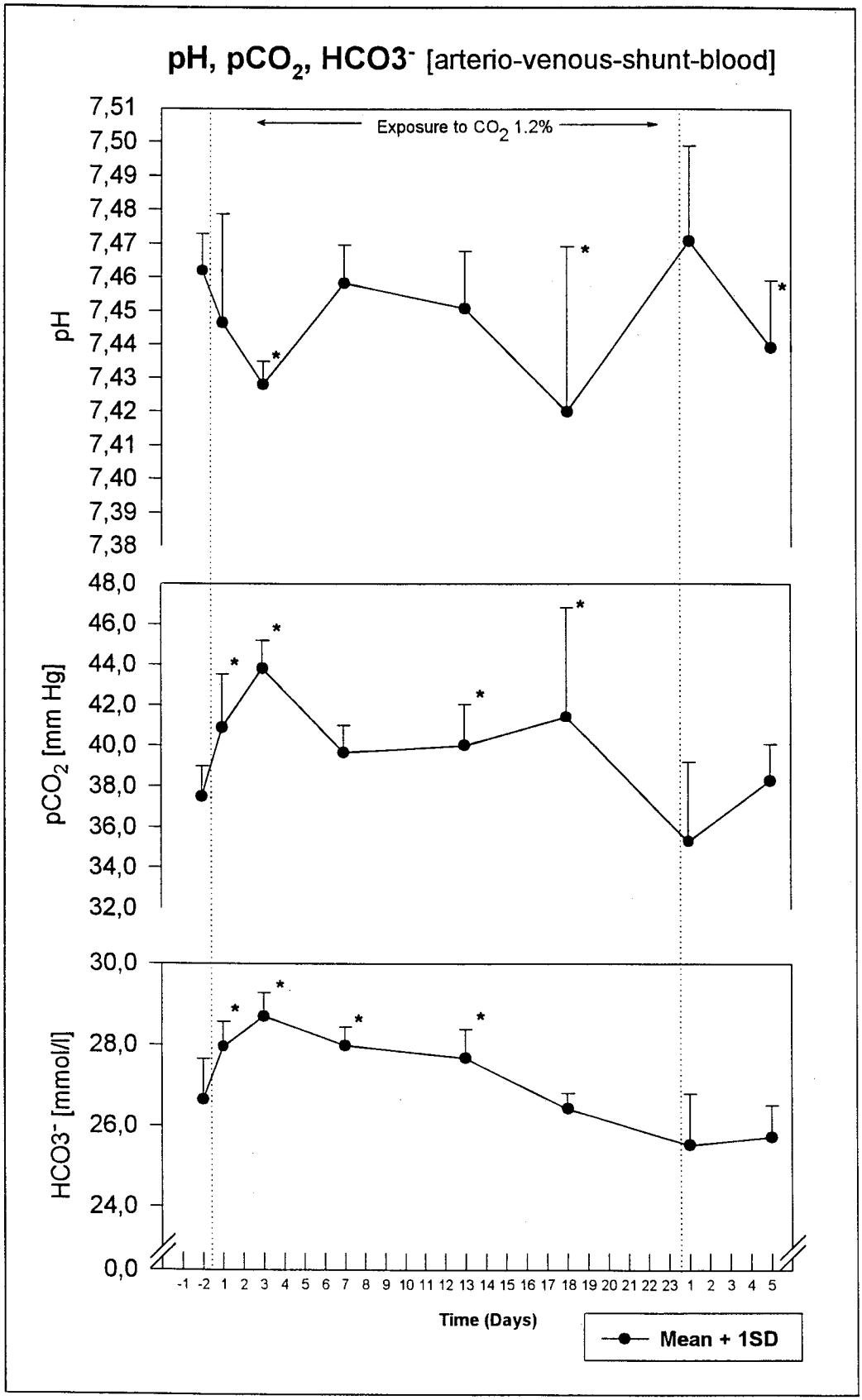

Cerebral Blood Flow Velocity (CBFv): Left Middle Cerebral Artery (MCA)
Mean CBFv MCA [cm/s]: 10° HDT + Rebreathing Test
Exposure to CO2
Mean CBFv MCA [cm/s]
130
120
110
100
90
80
70
0
-1 -2 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 1 2 3 4 5
Time (Days)
Mean + 1 SD; 0.7% CO2
Mean + 1 SD; 1.2% CO2

Fig 5


pH, pCO2, HCO3- [arterio-venous-shunt-blood]
Exposure to CO2 1.2%
pH
7,51
7,50
7,49
7,48
7,47
7,46
7,45
7,44
7,43
7,42
7,41
7,40
7,39
7,38
pCO2 [mm Hg]
48,0
46,0
44,0
42,0
40,0
38,0
36,0
34,0
32,0
HCO3- [mmol/l]
30,0
28,0
26,0
24,0
0,0
-1 -2 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 1 2 3 4 5
Time (Days)
Mean + 1SD