The Cardiovascular and Respiratory Responses to CO₂ under Hyperventilation and Posture Change in Parkinson’s Patients

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Abstract—In this paper, study is focused on patients with autonomic dysfunction, such as Parkinson’s disease, and how the interaction between cerebral autoregulation and ventilatory control is affected under hyperventilation and posture changes. Experiments were designed with 13 healthy youth subjects, 10 healthy elder subjects, and 13 subjects with Parkinson’s disease (PD) to acquire cardiovascular and respiratory signals during supine, head-up tilt (HUT), and hypocapnia. Signal processing is performed to obtain the end-tidal partial pressure of carbon dioxide (P_{ETCO₂}) throughout the hypocapnic range and their corresponding cardiovascular and respiratory signals, including mean systolic blood pressure (MSBP), mean arterial blood pressure (MABP), mean heart rate (MHR), mean breathing rate (MBR), and mean cerebral blood flow velocity (MCFBV). Analysis was further achieved to study the variations in parameters to changes in P_{ETCO₂} and to depict their variation over time. The results of the different analysis all pointed to suggesting that although Parkinson’s patients still retain some form of cerebral auto-regulation, they do not have the range of blood flow regulation that a healthy subject does and reactivity to CO₂ is limited to a smaller range.

Index Terms—autonomic dysfunction, Parkinson’s disease, hyperventilation, posture changes, cerebral blood flow

I. INTRODUCTION

One of the many health issues that come with old age is the degradation of the nervous system. When the nerves degrade, they are no longer able to function at full capacity and the nerves lose their mass and have defects in their structure, which leads to a reduced impulse transmission time [1]. The impairment or malfunction of the autonomic nervous system is known as dysautonomia or autonomic dysfunction. Some of the symptoms that suggest autonomic insufficiency are lightheadedness from standing up, heat intolerance, loss of bladder and bowel control, or erectile dysfunction. As blood pressure rises, the amount of blood flow in the brain is restricted as to prevent over-perfusion. The restriction in blood flow is accomplished by changing blood vessel diameter and increasing resistance. There are many mechanisms contributing to the regulation of cerebral blood flow [2], but this study will largely focus on the chemical influence.

The relationship between middle cerebral artery (MCA) blood velocity and end-tidal partial pressure of carbon dioxide (P_{ETCO₂}) throughout the hypocapnic-hypercapnic range in humans was examined in an earlier study [3]. The MCA peak blood velocity responses to 14 different levels of P_{ETCO₂} from 22 to 50 Torr were tested and the result showed that cerebral vasomotor reactivity (CVMR) were nonlinear with different sensitivities during hypocapnia and hypercapnia. Further analysis on the nonlinear responses of cerebral blood flow (CBF) to P_{ETCO₂} was performed [4]. Because arterial blood pressure (ABP) also affects CBF, the cerebral vasomotor reactivity index (CVC) was utilized instead of to eliminate effects of ABP and get a more accurate analysis of the response to P_{ETCO₂}. The MCA blood flow velocity and mean arterial blood pressure (MAP) changes to different P_{ETCO₂} were measured and studied in 16 healthy subjects to investigate the effects of ABP on CBF and its response to CO₂ along with the blood pressure component [5]. Different CO₂ concentration indicators, specifically end-tidal (P_{ETCO₂}), arterial (P_{ACO₂}), and internal jugular vein (P_{jvCO₂}) were investigated and their corresponding cerebrovascular reactivity were further studied [6]. The results revealed that P_{ACO₂} is overestimated by P_{ETCO₂} during hypercapnia but not hypocapnia, thus underestimating CVMR. With regards to P_{jvCO₂}, while the results indicate that reactivity is higher, without further clarification as to the mechanisms of CO₂ flux across the brain, the actual physiological significance of CVMR may be unclear. A study on the effects of posture change on control of ventilation [7] was conducted to examine the ventilatory response to CO₂ during supine and 75° head-up tilt (HUT).
in 11 healthy male subjects. The results indicated that minute expiratory ventilation \( V_E \) and tidal volume \( V_T \) increased during HUT while \( P_{ETCO_2} \) and transcutaneous \( P_{CO_2} \) decreased. The changes in \( P_{CO_2} \), alveolar ventilation \( V_A \), and CBF velocity (CBFV) in the middle and anterior cerebral arteries were recorded for 15 subjects during HUT [8]. It was found that \( P_{CO_2} \) and \( P_{ETCO_2} \) decreased during HUT while increased. Also, CBFV decreased throughout HUT even after decreases in \( P_{CO_2} \) has become smaller. Based on these results, it was suggested that reductions in \( P_{CO_2} \) is not solely due to the increased and other factors in addition to \( P_{CO_2} \) play a role in the reduction of CBFV. Previous studies also depicted that altered CBF may be an important contributor to the disease states associated with an attenuated cerebrovascular responsiveness to CO2 [10].

Through the analysis of the cardiovascular and respiratory responses, the purpose of this study is to understand the effects of nerve degeneration on the human body focusing on the autonomic nervous system (ANS) during hyperventilation and posture change for ANS impaired patients. Specifically this study will be taking a look at how the how cerebral autoregulation (CA) and control of ventilation is affected in patients with degenerated nerves such as Parkinson’s. This will be accomplished by inducing changes in posture and CO2 in the patients and studying how CA and ventilatory parameters reacts to these changes compared to healthy subjects. From the results of the experiment and analysis, a better understanding of how the two auto-regulating systems of a patient with an impaired ANS responds when stressed will be gained.

II. METHODS

<table>
<thead>
<tr>
<th>Groups</th>
<th>Gender</th>
<th>Subjects</th>
<th>Age</th>
</tr>
</thead>
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<tr>
<td>Healthy-45°</td>
<td>M</td>
<td>4</td>
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<tr>
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<tr>
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<td>7</td>
<td>14</td>
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<tr>
<td></td>
<td>F</td>
<td>2</td>
<td>9</td>
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<tr>
<td>PD Patients</td>
<td>M</td>
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<td></td>
<td>F</td>
<td>6</td>
<td>12</td>
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</table>

A. Subjects

The subjects for this study were recruited from the database of patients from Cheng-Ching General Hospital (CCGH), Taichung, Taiwan. The subjects were classified into the groups of healthy elders over 45 years of age (Healthy-45°), healthy youths under 45 years of age (Healthy-45°), patients with Parkinson’s disease (PD). The basic information of subjects is shown in Table I. All healthy subjects have no history of cardiovascular, respiratory, or neurological conditions. Parkinson’s disease patients were evaluated based on the Unified Parkinson’s Disease Rating Scale. All of the subjects in this study have given their informed consent and the study has passed inspection by the institutional review board at CCGH and complies with human subject protection regulations laid out by Taiwan Ministry of Health and Welfare.

B. Experiment

The HR, ABP, CBFV, \( P_{ETCO_2} \), airflow, and were recorded for each subject throughout the experiment. Continuous ABP and HR were recorded using Finapres (Model 2300, Ohmeda, Englewood, CO) on the right hand middle finger of each subject. The height of the finger is kept at equal height with the subject’s heart, including during HUT. The Finapres device used in this study is fully automated to adjust pressure accordingly with the volume changes in the finger artery. However because of the adjustment movement, servo components were introduced into the recorded data. These servo components are removed using special techniques outlined in a previous study [11]. CBFV was measured using a Transcranial Doppler Ultrasound (TCD, EME TC2020, Nicolet Instruments, Warwick, UK) isolated at 5-MHz over the temporal window using an elastic headband. Continuous \( P_{ETCO_2} \) and airflow signals were recorded using a Capnography (Neoset, FS-01382, SPEGS Industries Ltd., Jerusalem, Israel). All signals were sampled at 60 Hz and recorded simultaneously to PC using LabVIEW® for offline analysis.

Subjects were examined on a motor-driven tilt-table able to change the position of a patient from supine to 70° head-up within 4 seconds. Before data acquisition began, subjects first relaxed in the supine position for 10 minutes. The subject’s ABP, CBFV, \( P_{ETCO_2} \), airflow, and heart rate (HR) were all recorded continuously throughout the protocol. First, the subject’s baseline data was recorded for 5 minutes at supine rest. Then the subject underwent voluntary hyperventilation in the supine position where the subject breathed in for 5 seconds and out for 5 seconds. The deep breathing hyperventilation phase lasted for about 1 minute or about 6 cycles after which the subject is allowed to breathe normally. After 5 minute of rest the subject is then tilted head-up by 75° for 10 minutes while breathing normally. At the end of the HUT, the subject is then returned to the supine resting position.

The experiment protocol and procedure conducted in this study are depicted in Fig. 1.

Figure 1. Experiment protocol.
C. Signal Processing

Prior to the temporal data analysis, the acquired signals from all subjects were processed with following steps, as were concluded in Fig. 2.

- Signals were recorded through Finapres, TCD, and Neoset based on experiment protocol.
- Acquired data were stored and servo components were removed.
- \( P_{\text{ETCO}_2} \) peak detection was based on finding the max point between sections. These sections were defined by intersects between a moving average curve and the \( P_{\text{ETCO}_2} \) signal where the first intersect was of a positive slope followed by one with a negative slope.
- \( P_{\text{ETCO}_2} \) peak interpolation was performed using cubic Hermite spline at 3 samples per second.
- Data points that exceeded the mean of 50 prior and 50 subsequent points by one standard deviation were replaced with the mean value.
- Mean \( P_{\text{ETCO}_2} \) during hyperventilation was calculated by taking only the first 3 minutes of hyperventilation.
- Lowest \( P_{\text{ETCO}_2} \) Section was found as the section of data during the 3 minutes lower than Mean \( P_{\text{ETCO}_2} \).
- Mean CBFV of the lowest Mean \( P_{\text{ETCO}_2} \) section was determined by taking the mean of the CBFV data corresponding to the section of lowest Mean \( P_{\text{ETCO}_2} \) found in the previous step.

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\Delta \text{CBFV} = \left( \frac{x-y}{y} \right) \times 100\% \ .
\]

D. Signal Analysis

Analysis of the data was performed using the LabVIEW® system design software. Before data analysis can begin, the continuous raw data acquired must be first organized and categorized into the respective groups and states. The average values of MAP, systolic arterial pressure (SAP), HR, CBFV, breathing rate (BR), and \( P_{\text{ETCO}_2} \) will be calculated for each group under each state (supine, hyperventilation, HUT). The mean changes in MABP, HR, SBP, BR, and CBFV between subject groups were examined in the time domain. Examining when these changes occur and how long it takes before physiological changes occur in response to stimulants, a different view on the mechanisms of regulation was seen.

III. RESULTS

The results of the changes to the cardio-respiratory parameters induced by the data acquisition protocol are shown in Table II for the three different groups of subjects included in the study. For the Healthy-45 group, \( P_{\text{ETCO}_2} \) had a mean baseline of 30.88 (mmHg) at rest, 13.20 (mmHg) during hyperventilation, and 28.24 (mmHg) during tilt-up. Mean systolic blood pressure (MSBP) was 123.75, 125.41, and 133.93 (mmHg) respectively. Mean arterial blood pressure (MABP) was 84.57, 84.05, and 96.95 mmHg respectively. Mean heart rate (MHR) was 65.80, 68.43, and 71.94 (b/min) respectively. Mean breathing rate (MBR) was 18.11, 38.82, 17.25 (breaths/min) respectively. Mean cerebral blood flow velocity (MCBFV) was 49.67, 45.50 (cm/sec) respectively. For the Healthy-45+ group, \( P_{\text{ETCO}_2} \) had a mean baseline of 28.03 (mmHg) at rest, 9.81 (mmHg) during hyperventilation, and 25.03 (mmHg) during tilt-up. The MSBP was 121.25, 125.41, and 130.39 (mmHg) respectively. The MABP was 88.45, 91.32, and 95.68 (mmHg) respectively. The MHR was 64.31, 73.49, and 68.20 (b/min) respectively. The MBR was 16.61, 29.63, 17.44 (breaths/min) respectively. The MCBFV was 39.00, 24.37, 38.68 (cm/sec) respectively. For the Parkinson’s disease (PD) group, \( P_{\text{ETCO}_2} \) had a mean baseline of 27.65 (mmHg) at rest, 9.81 (mmHg) during hyperventilation, and 25.03 (mmHg) during tilt-up. The MSBP was 121.25, 125.41, and 130.39 (mmHg) respectively. The MABP was 88.45, 91.32, and 95.68 (mmHg) respectively. The MHR was 64.31, 73.49, and 68.20 (b/min) respectively. The MBR was 16.61, 29.63, 17.44 (breaths/min) respectively. The MCBFV was 39.00, 24.37, 38.68 (cm/sec) respectively.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>( P_{\text{ETCO}_2} )</th>
<th>MSBP (mmHg)</th>
<th>MABP</th>
<th>MHR</th>
<th>MBR</th>
<th>MCBFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy-45</td>
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<tr>
<td>Healthy-45+</td>
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<tr>
<td>PD</td>
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</table>
A. Cardiovascular and Respiratory Responses to CO₂

In terms of changes in systemic cardio-vasculature, there did not seem to be any significant changes for the MABP of the HEALTHY-45 group over the range of end-tidal carbon dioxide levels obtained in this study of approximately between 5~40 mmHg. This coincided with the results from earlier study [12] in that below the level of 40 mmHg there seemed to be little to no changes at all for MABP. However, for the HEALTHY-45 group, there seemed to be almost a difference of 20% between the lowest and highest P\textsubscript{ETCO\textsubscript{2}} values. In Fig. 3, the cardiovascular and respiratory responses to CO₂, including variations of MSBP, MABP, MHR, and MBR (from top to bottom) were shown for three subject groups. In each parameter, the spread of data was relatively wide and shows no significant correlation between each parameter and P\textsubscript{ETCO\textsubscript{2}}.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>P\textsubscript{ETCO\textsubscript{2}} (mmHg)</th>
<th>MSBP (mmHg)</th>
<th>MABP (mmHg)</th>
<th>MHR (beat/min)</th>
<th>MBR (breath/min)</th>
<th>MCBFV (cm/s)</th>
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<tbody>
<tr>
<td>Healthy-45</td>
<td>30.88±2.77</td>
<td>123.75±11.44</td>
<td>84.57±8.97</td>
<td>65.80±8.56</td>
<td>18.11±2.58</td>
<td>49.67±15.28</td>
</tr>
<tr>
<td>Healthy-45</td>
<td>28.03±3.55</td>
<td>121.25±8.22</td>
<td>88.45±8.88</td>
<td>64.31±9.30</td>
<td>16.14±2.26</td>
<td>49.67±15.28</td>
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<tr>
<td>PD</td>
<td>27.65±4.56</td>
<td>122.41±21.24</td>
<td>85.92±15.1</td>
<td>69.16±12.63</td>
<td>17.34±3.92</td>
<td>36.95±12.22</td>
</tr>
</tbody>
</table>

B. Temporal Analysis for Cardiovascular and Respiratory Parameters

In this section, we show the temporal variation from baseline data of each cardiovascular and respiratory parameter, including P\textsubscript{ETCO\textsubscript{2}}, MSBP, MABP, MHR, and MBR, from Fig. 4 to Fig. 8, respectively. The percentage
change of each parameter was presented for rest, hyperventilation, and tilt-up from left to right, and for the HEALTHY-45°, HEALTHY-45°, and PD from top to bottom in each figure. For every individual group, mean values of 5 seconds of data were displayed for analysis. In Fig. 4, it clearly shows a drop in ΔETCO2 levels to below -60% for the HEALTHY-45°, below -50% for the HEALTHY-45°, and to below -40% for the PD. During tilt-up, ETCO2 levels initially dropped to below -20% for all groups and slowly rose over time where it seemed to level off at around -10% less than baseline.

Baseline changes for ΔMSBP, shown in Fig. 5, fluctuated between 5% to -5% and drops sharply at the beginning of hyperventilation to below -5% then rose quickly as hyperventilation progressed. ΔMSBP then reached peak value after approximately 100 seconds of hyperventilation after which ΔMSBP began to drop back down to baseline value with an oscillation effect for the HEALTHY-45°. For the PD, the ΔMSBP continuously rose throughout the hyperventilation period and continued to do so even after hyperventilation has stopped and peaked out at around 10%. During tilt-up, the healthy control group showed an increase of around 10% in ΔMSBP and while PD group showed the same change of around 10%, it dropped first by approximate 10% before rising back up to just above baseline. ΔMSBP changes, shown in Fig. 6, followed a similar pattern to that of ΔMSBP where there was a slight oscillation around -5% to 5% during rest for all groups. During hyperventilation, ΔMABP increased quickly to approximately 10% before dropping back down to resting levels in the HEALTHY-45°. For the HEALTHY-45°, ΔMABP remained relatively stable until the end of hyperventilation after which began to oscillate again. In the PD, however, MABP rose throughout hyperventilation and continued to increase after hyperventilation has ended to close to 20%. During tilt, both control groups had MABP rising above 10% while the PD also had a small rise to above baseline values.

As can be seen in Fig. 7, ΔMHR showed no significant fluctuations during rest for all the groups. However, during hyperventilation, ΔMHR increased to 20% for the HEALTHY-45°, 10% for both the HEALTHY-45° and PD. ΔMHR for all four groups dropped back down to baseline after hyperventilation had ended. All groups also showed an increase during tilt-up to just fewer than 10% for the HEALTHY-45° and greater than 10% for the PD group, while the HEALTHY-45° ΔMHR oscillated around 10%. Fig. 8 shows the ΔMBR over time that, due to experiment protocol, the breathing rate during hyperventilation was increased by 100%. After hyperventilation had ended, the breathing rate returned back to baseline values. During head up tilt, although hard to see due to the scale, the ΔMBR rose slightly to around 7% for the HEALTHY-45° and around 4% for the PD group while values for the HEALTHY-45° remained close to the baseline.
C. Temporal Analysis for Cerebral Blood Flow

In Fig. 9, the variation of MCBFV was depicted for temporal analysis of PD in comparison with healthy subjects. At rest, the **Healthy-45°** showed continuous changes within the range from 10% to -10% while the **Healthy-45°** and PD showed changes but to a lesser degree. During hyperventilation, all groups displayed a rapid drop in ΔMCBFV, by -40% for the healthy groups, and by -20%~30% for the PD. After hyperventilation had ended at approximately time 175 (sec.), ΔMCBFV of all groups returned to baseline values. However, the PD showed a faster rise in ΔMCBFV but overshoot the baseline to 20% before lowering back down to baseline values. The healthy groups showed a gradual increase back to baseline values. During tilt all groups showed an initial drop with the ΔMCBFV of the **Healthy-45°** slowly climbing back up to baseline values while the **Healthy-45°** continued dropping throughout tilt-up. For the PD, ΔMCBFV remained slightly under baseline for the duration of the tilt-up phase.

IV. DISCUSSION AND CONCLUSION

Comparison of MABP between the results of this study and earlier finding [12], it seemed to be consistent between the two for levels below 40 mmHg. Both studies showed that with lower levels of $P_{\text{ETCO}}$, MABP did not change relative to the baseline. Not only was this true for healthy subjects, but it was also true for subjects with Parkinson’s disease. This suggested that vessel reaction to changes in $P_{\text{ETCO}}$ was the same without any impairment even in subjects with Parkinson’s disease.

Comparing the breathing parameter of MBR between healthy elderly group and the Parkinson’s group, there also were not any differences regarding the range of changes at the different levels of $P_{\text{ETCO}}$.

In terms of $P_{\text{ETCO}}$, there seemed to be no clear difference in the rise and fall over time between the healthy groups and the PD. However, the results showed that the range of the change during hypocapnia was greater in the healthy youth group than in the PD-group. This suggested that the regulation of $P_{\text{ETCO}}$ might have been impaired leading to a greater reactivity to $P_{\text{ETCO}}$ and thus a more limited range. During head up tilt, similar to other experimental results [13], there was a decrease in $P_{\text{ETCO}}$ from baseline of around 5% to 10% and did not return to baseline values until tilt-up has ended. This decrease might be explained by the approximately 1 breath per minute increase in breathing rate during tilt-up, but without knowing if ventilation has increased, there is no way of making certain if the fall in $P_{\text{ETCO}}$ can be for sure attributed by an increase in ventilation.

Regarding systemic hemodynamic changes over time, intracranial pressure appeared to have been decreased due to hyperventilation that in turn caused MCBFV to fall, and consequently the body compensated by increasing blood pressure and heart rate. Current results for the healthy elders coincided with other finding [4]. However, for the healthy youth group, blood pressure remained relatively unchanged and only compensated for the changes in MCBFV by increasing HR. For the PD group, it would seem that ABP and HR both attempted to compensate for the drop in CBFV during hyperventilation, but overcompensated and ABP continued to rise after hyperventilation ended. The overcompensation caused CBFV to overshoot before returning to the baseline. This suggested that PD patients might have some form of regulation impairment which was causing ABP to continue to rise even though HR had already stopped rising and led to overcompensation of CBFV past the baseline. This impairment was further supported by the results from tilt-up testing. The healthy groups showed the normal response where the blood pressure and heart rate increased to overcome the drop in CBFV caused by the cerebral pressure drop due to the change in posture. However for the PD group, even though heart rate increased as it would in a normal response, blood pressure dropped after tilt-up but only increased until baseline where it remained throughout the duration of tilt-up. This caused CBFV to remain below baseline which once again suggested the impairment of CA.

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REFERENCES


[Shyan-Lung Lin] was born in Taiwan on January 22, 1963. After graduated from E.E. Department of Ming Chi Institute of Technology, Taiwan, and finished his Navy ROTC service in 1983 and 1985, respectively, he earned his M.S. in Electrical and Electronic Engineering at North Dakota State University, Fargo, USA in 1988 and received his Ph.D. in Electrical Engineering and Computer Science at Northwestern University, Evanston, Illinois, USA in 1992. She joined Department of Automatic Control Engineering, Feng Chia University, Taichung, Taiwan in 1992 as an Associate Professor. Since 2014, Dr. Lin is also a joint Associate Professor in Department of Information Communication at MingDao University, Changhua, Taiwan. His research specialty includes respiratory control, biomedical control and simulation, numerical and parallel computations. Prof. Lin has published over 150 papers in refereed journal and conference and participated over 40 grant-projects from National Science Council, Taiwan, during the past 20 years.