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Nonlinear, multiple-input modeling of cerebral hemodynamics during baseline and hypercapnia in young and post-menopausal women

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***Abstract*— Normal aging is associated with changes in the cardiovascular system and more specifically in cerebral circulation. Sex-dependent changes in cerebrovascular CO_2 reactivity, which may be related to hormonal levels, have been also reported. We therefore examined cerebral hemodynamics, i.e., dynamic pressure autoregulation and CO_2 reactivity, by employing beat-to-beat values of mean arterial blood pressure and middle cerebral artery blood flow velocity, as well as breath-to-breath values of end-tidal CO_2 tension during baseline and sustained, end-tidal forcing induced hypercapnia in pre- and post-menopausal women. For this purpose, we employed a recently proposed nonlinear, multiple-input model of cerebral hemodynamics. The results suggest that dynamic autoregulation and reactivity in response to spontaneous fluctuations are not affected in postmenopausal women and that CO_2 reactivity to the larger, experimentally-induced hypercapnic stimuli are affected mildly. A significant decrease in CO_2 reactivity to spontaneous fluctuations was also observed during hypercapnia in all three groups.**

I. Introduction

Transcranial Doppler ultrasound (TCD) has been used extensively to assess cerebral blood flow velocity (CBFV) dynamics as well as their relation to both arterial blood pressure (ABP) and end-tidal CO_2 ($ETCO_2$) dynamics. Since normal aging is associated with changes in the cardiovascular system (i.e., increased systolic ABP and decreased baroreceptor sensitivity) and the cerebral vasculature (i.e., decreased CBF and pulsatile blood flow), the effects of aging on dynamic cerebral autoregulation have been studied by using beat-to-beat values of mean ABP (MABP) and mean CBFV (MCBFV), with the results suggesting an intact dynamic autoregulation [1]-[3]. The effects of aging on cerebrovascular CO_2 reactivity have been also studied, with different studies reporting intact and reduced reactivity [4]-[6]. Finally, sex-dependent, age-related changes in CO_2 reactivity have been reported [6].

Dynamic cerebral autoregulation has been studied by use of spontaneous beat-to-beat MABP and MCBFV fluctuations, revealing its frequency-dependent nature [7], [8]. More recently, it has been shown that spontaneous breath-to-breath $ETCO_2$ tension (P_{ETCO2}) variations and dynamic nonlinearities have a significant effect in the very low frequency range (<0.04 Hz), by employing a nonlinear, multivariate technique [9], [10]. In the present study, we employed the latter methodology to examine whether cerebral hemodynamics, i.e., dynamic pressure autoregulation and CO_2 reactivity, are affected in postmenopausal women during baseline and hypercapnic conditions. Since post-menopause changes in CBF may be related to hormonal levels [6], [11], we examined postmenopausal women that were and were not receiving hormonal therapy.

II. Methods

A. Experimental data

Six premenopausal (preM - 27.0±7.1 yrs, mean±SD) and thirteen postmenopausal women (54.0±3.6 yrs), six of whom were receiving hormonal therapy for at least 1 year (PM-HT; 54.7±2.4 yrs) and seven who were not (PM-noHT; 53.4±4.4 yrs) gave informed consent to participate in this study, which was approved by the University of Calgary Conjoint Health Research Ethics Board. The preM women were tested in the follicular phase of the menstrual cycle. None of the subjects were taking medication (except HT), all were nonsmokers, and none had a history of cardiovascular, cerebrovascular, or respiratory disease.

Each subject was positioned semisupine and TCD was used to obtain CBFV measurements from the right middle cerebral artery (MCA) using a 2-MHz pulsed Doppler

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ultrasound system (TC22, SciMed, Bristol, UK). The MCA was identified using an insonation pathway through the right temporal window just above the zygomatic arch. The Doppler system was adapted to output signals associated with the maximum and intensity-weighted mean frequency shifts, which were updated each time a new spectrum was calculated (every 10ms). For each 10-ms sample, the value for the blood velocity associated with the maximum frequency of the Doppler shift was calculated and recorded.

After taking resting measurements of P_{ETCO2} and end-tidal O_2 tension (P_{ETO2}) for approximately 10 min, dynamic end-tidal forcing was used to control both. The protocol, shown in Fig. 1 for a representative preM subject, consisted of a 10 min period, when mean P_{ETO2} was held constant at 88 mm Hg and mean P_{ETCO2} was held 1.0 mm Hg above the subject's natural resting value, followed by 20 min of hypercapnia, when mean P_{ETCO2} was held 8 mm Hg above resting levels and a 10 min period when mean P_{ETCO2} was held to its pre-hypercapnic value. ABP was monitored with finger photoplethysmography (Portapress, TPD Biomedical Instrumentation, The Netherlands).

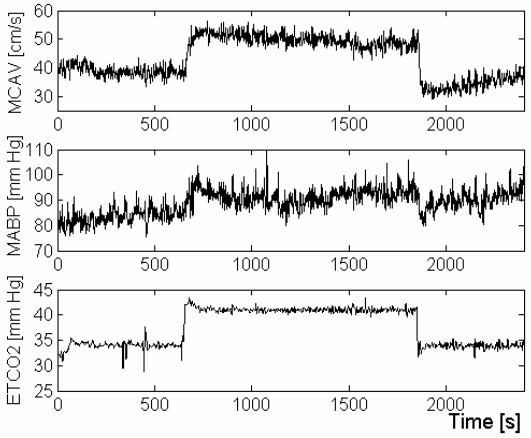

Fig. 1. Representative segments of experimental data for one preM subject. Bottom: P_{ETCO2}, Middle: MABP, Top: MCAV. The initial 10min of rest were followed by 20 min of hypercapnia (P_{ETCO2}=+8mm Hg compared to resting value) and 10 min of return to baseline.

Beat-to-beat mean values of mean ABP (MABP) and MCA velocity (MCAV) were calculated by integrating the waveform of the sampled signals within each cardiac cycle. The beat-to-beat values of MABP and MCAV and the breath-to-breath values of P_{ETCO2} were then interpolated and resampled at 1 Hz to obtain equally spaced time series data.

B. Mathematical Methods

The presence of significant nonlinearities in cerebral hemodynamics is well established [7]-[10]. Therefore, we employed a multiple-input, general Volterra model of cerebral hemodynamics in order to quantitatively describe the dynamic effects of spontaneous MABP and P_{ETCO2} changes on MCAV variations [9]:

$$MCAV(n) = \sum_{q=0}^{Q}\left\{\sum_{m_1}\cdots\sum_{m_q} k_{qi}(m_1,..,m_q)x_i(n-m_1)\ldots x_i(n-m_q)\right\} = \quad (1)$$
$$k_{0i} + \sum_{m} k_{1i}(m)x_i(n-m) +$$
$$+ \sum_{m_1}\sum_{m_2} k_{2i}(m_1,m_2)x_i(n-m_1)x_i(n-m_2) + \ldots$$

where *i:* MABP, CO_2. The linear (q=1) and nonlinear (q>1) Volterra kernels k_{qi} describe the linear and nonlinear effects of MABP (dynamic pressure autoregulation) and P_{ETCO2} (dynamic CO_2 reactivity) at time lags (m_1,...,m_q) before the present time lag n on MCAV respectively. The Volterra kernels were estimated on the basis of the MABP, P_{ETCO2} and MCAV data, by employing the Laguerre expansion technique [12] and the Laguerre-Volterra network methodology, which combines Laguerre functional expansions and Volterra-type networks (i.e., networks with polynomial activation functions) and has been shown to yield accurate models of nonlinear systems from short input-output records [13], [14]. The structural parameters of the nonlinear models (i.e., number of Laguerre functions and system order) were selected on the basis of the normalized mean-square error (NMSE) of the output prediction, which is defined as the sum of squares of the model residuals (the difference between the model prediction and the true output) divided by the sum of squares of the de-meaned true output. The statistical significance of the reduction achieved in the prediction NMSE for a model structure of increased order/complexity was assessed by comparing the percentage NMSE reduction with the a-percentile value of a chi-square distribution with p degrees of freedom (where p is the increase of the number of free parameters in the more complex model) at a significance level a of 0.05.

Dynamic pressure autoregulation and CO_2 reactivity in response to spontaneous fluctuations around the mean were assessed from six-minute (i.e., 360 points) MABP, P_{ETCO2} and MCAV data segments after high-pass filtering at 0.005 Hz in order to remove very slow trends. Furthermore, CO_2 reactivity to the hypercapnic step was assessed from the entire P_{ETCO2}-MCAV data sets, after low-pass filtering at 0.04 Hz.

III. Results

A. Hemodynamic signals

The steady-state values of MABP, P_{ETCO2} and MCAV during the three experimental periods, i.e., baseline, hypercapnia and post-hypercapnia, are shown in Fig. 2 averaged over all subjects (mean±SE). MABP and MCAV during baseline were not significantly different between groups, while P_{ETCO2} was higher in PM-noHT women. All hemodynamic signals increased significantly during hypercapnia. MCAV decreased significantly post-hypercapnia compared to hypercapnia, while the corresponding decrease in MABP was significant only in PM-HT women. However, both remained significantly

higher than baseline, in contrast to P_{ETCO2}.

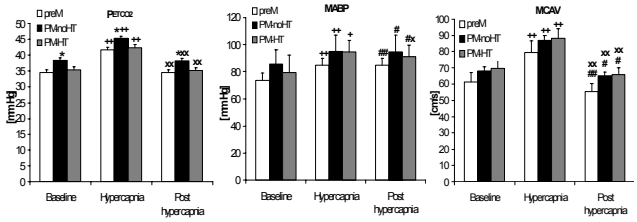

Fig. 2. Hemodynamic signals during baseline, hypercapnia and post-hypercapnia. *: P<0.05 PM-noHT vs preM. **+:** P<0.05, ++: P<0.01 hypercapnia vs. baseline. **#:** P<0.05, ##: P<0.01 post-hypercapnia vs. hypercapnia. **x**: P<0.05, **xx**: P<0.01 post-hypercapnia vs. baseline.

B. Analysis of spontaneous fluctuations around the mean

Nonlinear terms improved the model prediction NMSE error in all cases (average NMSE reduction over 15% compared to linear models). Dynamic pressure autoregulation was assessed by the MABP kernels $k_{i\text{MABP}}$, while dynamic CO_2 reactivity was assessed by the P_{ETCO2} kernels $k_{i\text{CO2}}$. The linear component of dynamic pressure autoregulation (i.e., $k_{1\text{MABP}}$), is shown in Fig. 3 in the frequency domain, averaged over all preM subjects (solid line) along with its corresponding standard error (dashed lines). As expected, it exhibits a high-pass characteristic during baseline, suggesting that slow MABP fluctuations are attenuated more effectively, which was preserved during hypercapnia and post-hypercapnia. $k_{1\text{MABP}}$ was found to be similar in the PM-noHT and PM-HT groups (data not shown), suggesting that dynamic pressure autoregulation was not impaired in post-menopausal women. The linear component of dynamic CO_2 reactivity $k_{1\text{CO2}}$ is shown in Fig. 4 in the time domain (preM subjects; solid line: average, dashed lines: standard error). Its form was also found to be similar between all three groups. In the frequency domain, it exhibited a low-pass characteristic with significant gain values below 0.04 Hz, i.e., spontaneous P_{ETCO2} changes account for a significant fraction of the very slow spontaneous MCAV variability. The decrease in reactivity to spontaneous CO_2 changes during hypercapnia (Fig. 4, middle panel) was observed in all groups, concurrent with a reduction in low-frequency MCAV variability.

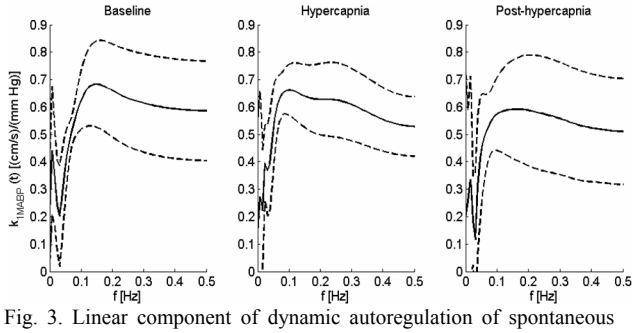

Fig. 3. Linear component of dynamic autoregulation of spontaneous MABP changes ($k_{1\text{MABP}}$) in the frequency domain (preM women). $k_{1\text{MABP}}$ was found to be similar between groups, as well as during different experimental conditions, exhibiting a high-pass characteristic in all cases.

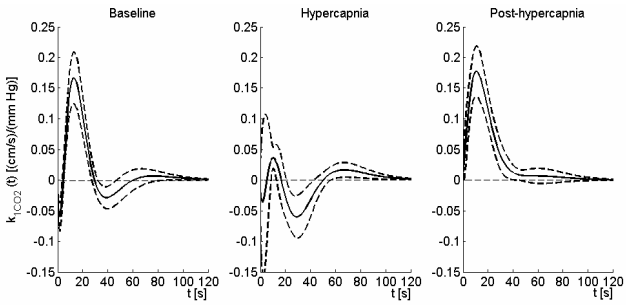

Fig. 4. Linear component of dynamic reactivity to spontaneous P_{ETCO2} changes around the mean ($k_{1\text{CO2}}$) in the time domain (preM women). $k_{1\text{CO2}}$ was found to be similar between groups, with the decrease during hypercapnia observed in all three groups.

C. Dynamic CO_2 reactivity to the hypercapnic step

Since in this case we employed the entire low-passed P_{ETCO2} and MCAV time-series to estimate the CO_2 kernels in a one-input context, the prediction NMSEs achieved by linear and nonlinear models were considerably lower than in the case of spontaneous fluctuations (from as low as 2% to 20%), since the major fraction of the very low frequency MCAV power is accounted for by the hypercapnic step. The average NMSE reduction achieved by using nonlinear models was considerable in this case also (around 5%). The linear kernels $k_{1\text{CO2}}$ are shown in Fig. 5 for all three groups. Their form was generally similar between groups, however a decrease was observed in their slow component, i.e., kernel values after 40s, in PM women (Fig. 5, middle and right panels). Note also that the kernels of Fig. 5 were similar to their counterparts obtained from spontaneous fluctuations around the mean during baseline (Fig. 4, left panel).

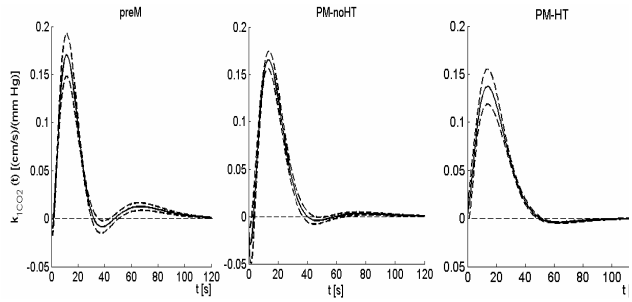

Fig. 5. Linear component of dynamic CO_2 reactivity to the hypercapnic step. Note the reduction in the slow component in both PM groups compared to the preM group.

IV. DISCUSSION AND CONCLUSIONS

The main findings of the present study were the following: dynamic pressure autoregulation and CO_2 reactivity in response to spontaneous MABP and P_{ETCO2} fluctuations around the mean were found not to be affected in post-menopausal women. Regarding dynamic pressure autoregulation, our results agree with previous studies that have reported intact autoregulatory capacity in normal aging, as well as in hypertensive subjects, during both resting conditions and orthostatic stress [1]-[3]. To our knowledge, the effect of aging on dynamic CO_2 reactivity to

spontaneous variations around the mean has not been studied before.

Dynamic CO_2 reactivity to the hypercapnic step was also found to be similar in PM women, except a moderate decrease observed in its slow component. Previous studies of reactivity to step CO_2 changes in aging have yielded controversial results [4]-[6]. Furthermore, the fact that the linear CO_2 kernels obtained from spontaneous and step hypercapnic data were found to be similar (Fig. 4, left panel and Fig. 5) implies that sensitivity of the cerebral vasculature to small CO_2 variations around the mean, as well as larger, externally-induced CO_2 changes, is comparable in terms of magnitude values. It also reflects the fact that the major fraction of P_{ETCO2} spectral power lies in the very low frequency range (i.e., 0.04 Hz), therefore the estimates obtained from the low-passed data sets are not affected to a large extent.

Dynamic autoregulation of spontaneous MABP changes was found not to be affected considerably during hypercapnic conditions in all three groups. On the other hand, dynamic CO_2 reactivity was found to be decreased during hypercapnia both in preM and PM women. This is possibly due to that the vasodilation induced by hypercapnia reduces the reactivity of cerebral vessels to small CO_2 changes.

Employing a nonlinear, multiple-input methodology is important in order to obtain accurate models that reflect hemodynamics under rest, since nonlinearities and CO_2 explain a significant fraction of slow MCAV variability. If either is not taken into account, the estimates of dynamic autoregulation and/or CO_2 reactivity may be affected [9].

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