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Attn: Preeclampsia Foundation
Re: Vision Grant
Awardee: Richard Burwick, MD, MPH

Mid-Cycle Progress Report

The primary aim of our project, "Complement in the Brain and its Association with Centrally Mediated Hypertension and Sympathetic Nerve Activity in Preeclampsia", is to determine if blood brain barrier impairment is increased in preeclampsia and whether such impairment correlates with central inflammation. We hypothesized that inflammatory mediators, specifically activated complement proteins, mediate hypertension and sympathetic nerve activity centrally. To address this research question, we designed experiments in human and rodent pregnancies. This mid-cycle report addresses updates from Aim 1, the human arm of the study.

Institutional review board approval for our study in human subjects was obtained at Oregon Health & Science University. The study was termed the Brain Complement and Preeclampsia (BCP) study. To-date 57 pregnant subjects have been enrolled in the BCP study. Target enrollment to achieve the primary study aim is 15 non-hypertensive control subjects and 15 preeclampsia subjects with paired blood and spinal fluid. Of 57 enrolled subjects, 37 have completed paired collection of blood and spinal fluid at time of delivery, including: non-hypertensive controls (n=14), chronic hypertension (n=5), gestational hypertension (n=7), and preeclampsia (n=11). Subject characteristics are shown in Table 1.

To assess sympathetic nerve activity in human subjects, we have measured heart rate variability (RR interval) in all enrolled subjects before and after delivery, as shown in Figure 1. RR interval is reduced with increased sympathetic activity. This measure will allow to correlate spinal fluid markers and blood brain barrier impairment with maternal sympathetic activity in preeclampsia versus non-hypertensive controls. After we meet target subject enrollment, we will measure the following proteins in blood and spinal fluid: albumin, C5a, C5b-9, IL-6 and TNF-α. These measurements will allow us to test the hypotheses in Aim 1, that blood brain barrier impairment, and central inflammation, is increased in preeclampsia compared to non-hypertensive controls. Subsequently in Aim 2, we will test our hypotheses in pregnant rats with and without preeclampsia [reduced uterine artery perfusion pressure (RUPP)model], through similar tests of blood and spinal fluid. Finally, we will test whether complement blockade reduces blood pressure and sympathetic nerve activity in the RUPP rat.

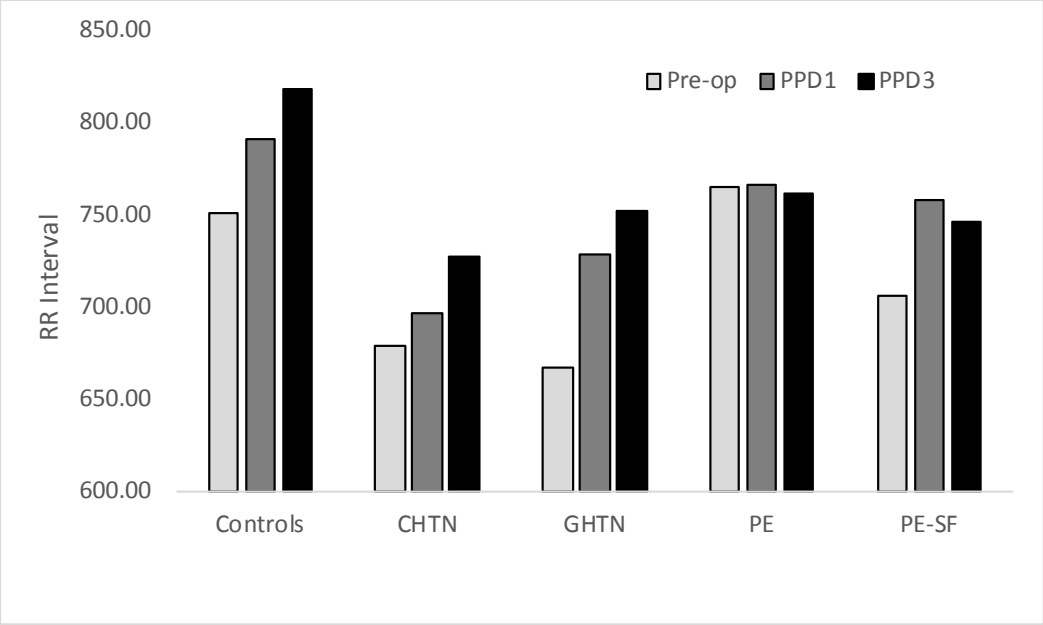
Table 1.

Characteristic	Controls*	CHTN	GHTN or PE	PE-SF
Gestational age at enrollment (wks ± SD)	37.8 ± 1.3	37.3 ± 1.2	37.6 ± 1.8	32.5 ± 3.8
Maternal age (yrs ± SD)	32.9 ± 5.7	36.3 ± 5.7	33.8 ± 5.6	31.6 ± 5.9
BMI (kg/m^2 ± SD)	32.3 ± 6.5	48.0 ± 10.1	38.4 ± 7.9	34.8 ± 7.3
Systolic blood pressure (mm Hg ± SD)	126 ± 7.4	151 ± 8.1	151 ± 9.9	175 ± 16
Diastolic blood pressure (mm Hg ± SD)	79 ± 7.7	94 ± 12	98.2 ± 11	116 ± 13

*Control subjects without hypertension

CHTN, chronic hypertension; GHTN, gestational hypertension; PE, preeclampsia; PE-SF, preeclampsia with severe features

Figure 1. RR Interval as a Measure of Sympathetic Nerve Activity, by group, before and after delivery



CHTN, chronic hypertension; GHTN, gestational hypertension; PE, preeclampsia; PE-SF, preeclampsia with severe features; PPD2, postpartum day 2; PPD3, postpartum day 3