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Hemodynamic and ocular responses to caloric stimulation and age-related disparities

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HEMODYNAMIC AND OCULAR RESPONSES TO CALORIC STIMULATION AND AGE-RELATED DISPARITIES

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ABSTRACT

Age-related declines in vestibular function affect balance and coordination in older adults. Of perhaps equal importance, but less understood, are the potential implications of vestibular degeneration on cardiovascular homeostasis. Recent evidence suggests that the semi-circular canals, a section of the vestibular system, may be involved in the vestibulosympathetic reflex (VSR), but the extent to which the aging of the semi-circular canals interferes with cardiovascular homeostasis is unknown. Activation of the intact VSR results in increases in tonometric blood pressure (TBP) and heart rate (HR) as well as decreases in cardiac output (Q) and pre-ejection period (PEP). The purpose of this investigation was to observe reflexive changes in the VSR and cardiovascular function during activation of the horizontal semi-circular canals using bithermal binaural caloric irrigation in young (n =11; 18-39), middle-aged (n = 7; 40-64), and old (n = 9; 65+) adults and to describe age-related changes in cardiac dynamics in order to identify a possible indicator of disease and/or disease risk. 3x2 repeated measures ANOVAs revealed significant increases in slow-phase velocity for all subjects under all conditions, which indicate adequate excitation of the semi-circular canals to stimulate the VSR; TBP increased in the young and middle-aged groups to a greater degree than the old group; RR-intervals tended to decrease in young adults while either decreasing to a much lesser extent or increasing in the middle-aged and old groups. A decrease in RR-intervals indicates an increase in heart rate, and, thus activation of the VSR. Similarly, sympathovagal balance consistently increased in young participants but not in the old adults. These preliminary results cannot confirm an age-related deterioration in semi-circular canal control of cardiovascular function; however, they are sufficient to underscore the importance of the continued investigation of age-related changes in the VSR.

CHAPTER 1 - INTRODUCTION

Stability and balance problems, as well as fall risk, are more pronounced in the elderly and appear to occur as common manifestations of biological aging. One emerging area of interest is the age-related decay in the number of neurons in the vestibular nucleus[1], which likely impacts balance, coordination, and other physical function characteristics[1,2,3]. Moreover, the decrease in functionality of the vestibular system may be a contributor to the increase in frequency of falls with age[4,5]. Falls in the elderly lead to increased morbidity and mortality rates[6,7] due to deterioration of overall health or other complications such as depression due to lack of mobility and ability to live dependently or infection.

Human aging is also associated with deterioration in the function of a variety of reflexes thought to be important for maintaining cardiovascular homeostasis, including the vestibulosympathetic reflexes (VSR). Of particular relevance here are the vestibulocardiac reflexes, which are believed to play a role in combating orthostatic hypotension[8,9,10], a common problem in older adults, and may exacerbate dangerous cardiac rhythm disturbances. Recent evidence from our lab suggests that the semi-circular canals may be involved in the VSR, but the extent to which the aging of the semi-circular canals interferes with cardiovascular homeostasis is unknown.

1.1 Vestibulosympathetic Reflex (VSR)

The VSR involves sympathetic nerve stimulation by the vestibular system through engagement of the semi-circular canals and/or otolith organs. Animal studies indicate that the VSR assists in blood pressure regulation during orthostasis[8]. Activation of the intact vestibular system clearly revealed sympathetic activation[9], thereby suggesting a pathway through which vestibular function assists in regulation of blood pressure. This has implications for human

aging, which has also been associated with an increased risk of orthostatic hypotension[10]. In the elderly it is quite possible that part of the cause of orthostatic hypotension is due to problems with the vestibular system – specifically an attenuated VSR, which has been linked with reductions in arterial pressure[10,11]. This suggests that the VSR plays a role in blood pressure regulation[12], possibly explaining increases in orthostatic hypotension when combined with the diminished physiologic responses due to the morphological changes associated with aging[2,13,14].

This VSR has been confirmed in humans, primarily inferred from increased muscle sympathetic nerve activity (MSNA) and skeletal muscle vasoconstriction observed during head down rotation (HDR)[8,15,16]. Furthermore, data indicate that the VSR remains intact during unloading of the cardiopulmonary baroreceptors, and that the influence of the vestibulo- and baroreflexes are additive[16]. These latter findings have led scientists to surmise that the vestibular organs provide a potential feed-forward mechanism; that is an anticipatory mechanism for defending postural changes in blood pressure, prior to the unloading of the baroreceptors themselves.

Despite observing heightened MSNA and skeletal muscle vasoconstriction during HDR, some investigators have observed no increase in arterial blood pressure[9,15,16]. These findings have been interpreted to mean that while HDR causes skeletal muscle vasoconstriction, this is accompanied by vasodilatation of vascular beds other than in skeletal muscle and/or a decrease in cardiac output (Q). As to the former (i.e., possible vasodilatation of other vascular beds), while reflexive cholinergic responses have not been ruled out, investigators have yet to identify a specific vascular bed that dilates during HDR. As to the latter, one previous investigation[17] has inferred no significant change in Q from cardiothoracic impedance; however, this study, as well as published data from our laboratory reveal a decrease in RR-interval (increase in heart rate)[12,17]

and an increase in sympathovagal modulation of the heart[12] indicating that central cardiovascular function is influenced to some degree by HDR. Thus, while little debate exists as to the existence of sympathetic activation during stimulation of the vestibular system, the pattern of cardiovascular changes must be further elucidated to understand the role of the vestibular apparatus in regulation of arterial blood pressure.

1.2 Aging and the VSR

Human aging has long been associated with deterioration in vestibular system function, which is thought, as previously stated, to contribute to increased problems with stability and balance and increased incidence of falling. Experimental evidence suggests age-related changes in the morphology of peripheral and central aspects of the vestibular system[8,13,14,18]. These include a decrease in the number of hair cells in the otoliths[13] as well as a decrease in the number of kinocilia and stereocilia in existing hair cells[19]. In addition, aging is associated with a decrease in afferent fibers to the cristae and maculae[13,18], as well as degeneration of the otoconia of the maculae[20]. Concurrent with these morphological changes are functional changes, primarily noted as reduced vestibuloocular[21] and vestibulospinal[22] reflexes. Likewise, an age-related attenuation of the VSR has been uncovered[10,11]. Ray et al.[11] recently reported deterioration in the vestibulocardiac reflex with human aging with younger subjects (28 +/- 1 year) eliciting an average increase in total MSNA in the range of 85+/-16%, whereas the older subjects (64 +/- 1 year) nerve activity only increased by 12+/-5%. These investigators suggest that, along with the deterioration of cardiovascular reflexes, there is deterioration of the VSR, as seen by maneuvers designed to evoke the vestibular organs and cause otolith stimulation that accompanies unexpected drops in blood pressure in older subjects. Therefore, it has been hypothesized that vestibular aging has the potential to contribute significantly to the occurrence

and magnitude of orthostatic hypotension in older adults. While the specific mechanisms involved have not been clearly elucidated, it has been surmised that aging is associated with decreased ability to heighten total peripheral resistance (TPR) in response to sympathetic activation[10,11,23].

1.3 Semi-circular Canals and the VSR

While the semi-circular canals are known to be instrumental in balance and coordination, there are only two published studies to substantiate their role in autonomic control of cardiovascular reflexes. Cui et al.[24,25] found that cool and warm calorics, which solely stimulate the semi-circular canals, do elicit a sympathetic response. However, Costa et al.[26] and Ray et al.[27] observed no influence of cool calorics or yaw head rotation, respectively, on MSNA. Despite these conflicting, and minimal, findings, preliminary data from our laboratory reveal a significant decrease in heart rate variability (HRV) during active and passive high-frequency headshakes, suggesting a reduction in vagal modulation of the heart. Having observed similar results under both active and passive headshakes, we believe we will rule out skeletal muscle group III and IV afferents as playing a large role in the cardiovascular responses. However, visual inputs and changes in intracranial pressure cannot be ruled out as possible causative factors. Because of these possible issues, the fact that caloric stimulation solely excites the semi-circular canals (and not the otolith organs), the contradictory findings of Costa et al.[26] and Ray et al.[27] versus Cui et al.[24], as well as the possible lack of adequate stimulation by Ray et al.[27] and Costa et al.[26], we chose caloric stimulation over headshakes for this experiment.

In general, stimulation of the VSR is characterized by an increase in heart rate (HR) and blood pressure and a decrease in RR-interval (RR-I), stroke volume (SV), Q, and pre-ejection period (PEP). For further details, see Table 2.2 below.

1.4 Purpose

The purpose of this investigation is to observe reflexive changes in VSR and cardiovascular function during activation of the horizontal semi-circular canals using bithermal binaural caloric irrigation in young (n = 11; 18-39 years), middle-aged (n = 7; 40-64 years), and old (n = 9; 65+ years) adults. We are also going to describe any age-related changes in cardiac dynamics and autonomic modulation of the heart subsequent to maneuvers designed to isolate the influence of the vestibular horizontal semi-circular canals (i.e., bithermal binaural calorics) in order to identify another indicator of disease and/or disease risk.

1.5 Hypotheses

We hypothesize that we will observe an increase in sympathovagal balance (i.e., increased sympathetic and/or decreased parasympathetic modulation) of cardiac chronotropic activity such that excitation of the semi-circular canals will result in stimulation of the VSR yielding sympathetic activation. We also hypothesize that young subjects will have the greatest sympathetic activation from VSR stimulation and that the old subjects will have the poorest response to VSR stimulation. Such a hypothesis is consistent with other age-related changes in autonomic-mediated reflex mechanisms[28]. Specific expectations of responses are listed below in Table 2.1. Also, caloric stimulation should cause a significant increase in slow-phase velocity (SPV) in all subjects.

CHAPTER 2 - METHODS

2.1 Participants

Twenty-seven adults: young (n = 11; 18-39 years); middle-aged (n = 7; 40-64 years); and old (n = 9; 65+ years) adults with no symptoms of health problems or inner ear disorders were recruited to participate in this study. Exclusion criteria were any adults known to be at high risk for adverse responses of physical exertion according to the guidelines of the American College of Sports Medicine[29]. This includes patients with known severe coronary artery disease, chronic heart failure, ischemia at rest or with light exertion, and known survivors of sudden cardiac-death. In addition, patients with known diabetes, renal disease, and/or those taking chronic anti-depressants were excluded from the study. Finally, vestibular patients were excluded from the study.

2.2 Parameters of Focus

Table 2.1. HRV and other cardiac parameters of focus for all subjects and their expected responses to caloric stimulation.

Parameters of CV Responses	Description	Response to Activation of the VSR
LFNN	Low-frequency power normalized; LF/(Total power-VLF)*100	↑
LF/HF	The ratio of low-to-high frequency power; a spectral parameter of HRV	↑
RR-I	RR-Interval; Inversely related to HR	↓
pNN50	pNN50; the percentage of successive RRI differences exceeding 50 msec	↑
SV	Stroke volume; the quantity of blood pumped by the heart per cardiac cycle	↓
Q	Cardiac output; the amount of blood pumped by the heart per minute	↓
SBP	Systolic blood pressure; highest arterial blood pressure of a cardiac cycle	↑
DBP	Diastolic blood pressure; least blood pressure obtained during cardiac cycle	↑

(Table 2.1 cont.)

TBP	Tonometric blood pressure; non-invasive method for continuous measurement of pressure in closed vessels	↑
TPR	Total peripheral resistance; vascular resistance of the systemic circulation	↑
PEP	Pre-ejection period; interval from the onset of ventricular depolarization to the beginning of the opening of the aortic valve for left ventricular ejection	↓

2.3 Instruments

2.3.1 Health Screening Instruments

The PAR-Q and Health Status Questionnaires[30] were used to assess medical history and health risk factor status. An audiological case history was used to provide the examiner with a qualitative report of the participants' auditory and vestibular history[31].

2.3.2 Audiological and Vestibular Assessment

The otoscopic examination[31], immittance measures using a Maico 630 impedance bridge[32], pure tone audiometric evaluation using a Maico 40 air and bone audiometer[33], vestibulo-collic screening using a Biologic Auditory Evoked Potentials software[34], vertebral artery screening[35], cervicospinal screening[36], modified Dix-Hallpike maneuver[37], and oculomotor and positional subtests of electronystagmography[38] were performed according to standard clinical protocol for hearing and vestibular screenings. The Vestibular Disorders Activities of Daily Living (VADL)[39] and the Dizziness Handicap Inventory (DHI)[40] were used to assess the participants' subjective inner ear health.

2.3.3 Physiologic Signals

The electrocardiogram (ECG), electrooculograph (EOG), impedance cardiograph (IC), and heart sounds were collected and processed via *Biopac* data amplifiers and analog to digital board (Santa Barbara, CA). The *Biopac* signals were digitized and stored with the use of the companion *Acknowledge 3.7.2* software (Santa Barbara, CA). The tonometric blood pressure

(TBP) data were captured using the Colin 7000 TBP device (San Antonio, TX). This device also has a voltage output that was sent to the *Biopac* AD board and was digitized and stored in real time along with the other physiologic signals. The *Biopac* equipment for Q measurement incorporates a precision high-frequency current source, which introduces a very small (100μA rms or 400μA rms) current through the tissue being measured (heart and surrounding thorax tissue) with the volume being defined by the placement of a set of eight current source electrodes – two pairs on the neck and two pairs on the torso. The set of monitoring electrodes on the torso then measures the voltage developed across the tissue volume. Because the current is constant, the voltage measured was proportional to the characteristics of the biological impedance of the tissue volume. Other connections include ECG electrode leads and the TSD108 heart sounds microphone to the DA100 differential amplifier. Measurements were made continuously pre, during, and post irrigation.

2.3.4 Caloric Irrigator

To control for muscle stretch receptors of the neck, visual inputs, and changes in intracranial pressure as possible causative factors during headshakes, we utilized bithermal binaural caloric irrigation using an ICS NCA200 air caloric irrigator to induce caloric nystagmus.

2.4 Procedures

The screening session lasted about 60 minutes, and the testing session, usually done within a week of the screening session, lasted about 90 minutes. The data were collected at the research laboratory in the Health and Wellness Center of St. James Place.

2.4.1 Screening Session

The study was explained in detail to the participant, and informed consent was obtained prior to any of the following procedures. The participant answered questions regarding his or her

health status and inner ear history to insure that the inclusion/exclusion criteria and appropriate subject classification for the study were met. After completing the questionnaires and case history, the audiological and vestibular screenings were made by a certified clinical audiologist in accordance with accepted procedures.

2.4.2 Testing Session

The study procedure for this session was re-explained in detail. The participant was measured for height, weight, waist girth, and hip girth using standard laboratory techniques. Following this, the participant was prepared for the collection of physiologic signals in the following manner: the ECG signals required the placement of three Ag/AgCl electrodes on the participant's upper torso; IC required the placement of four pairs of Ag/AgCl electrodes: two on the lateral aspect of the neck and two on the lateral aspect of the lower torso separated by a distance of 17% of the subject's height[41]; EOG required the placement of three electrodes on the participant's head: one on the forehead and one on each side of the head in the area of the articulation of the temporal and sphenoid bones; the heart sounds monitor is a stethoscope that was fixed to the participant's torso with standard adhesive tape; for TBP measurement, a standard blood pressure cuff was placed on the upper left arm and was used to calibrate the TBP device that was attached to the left wrist – this TBP device provides a non-invasive continuous assessment of blood pressure as detected in the radial artery. These instruments were used to determine HR, HRV, TBP, SV, Q, systolic time interval (STI), PEP, TPR, and SPV. These variables were derived under the conditions described below.

2.4.3 Calorics

Four caloric irrigations: two with cool (24° C) air (one in each ear) and two with warm (50° C) air (one in each ear) were performed to measure the physiologic function of the

horizontal semi-circular canals[42]. EOG was used to monitor eye movement during standard clinical irrigation protocol[43] with the participant's trunk at a 30° angle (to align the horizontal canals parallel to the gravitational vector) while resting on an exam table with eyes closed. The air was aimed at the tympanic membrane for 60 seconds. The cool or warm air shrank or expanded, respectively, the fluid inside the horizontal canal. This caused an inhibitory or excitatory response in the vestibuloocular reflex (VOR), resulting in vertigo and nystagmus toward the excited ear when using warm air and away from the excited ear when using cool air. After-flow measures (following stimulation) were recorded for 40 seconds with the eyes closed (caloric nystagmus) using casual conversation to eliminate cognitive interference, then the subject fixated for 20 seconds on a target located directly above his or her head on the ceiling to suppress remaining nystagmus. There was a 3 minute rest period prior to the first condition and following the remaining conditions. The order of cool/warm trials was randomized among subjects.

2.5 Analysis

2.5.1 Data Reduction

The data for each caloric condition was separated into two time frames: "pre", which was the 3 minute rest period prior to the condition; and "post", which included the 40 second task and 20 second fixation periods as well as some of the caloric condition. These two time frames were further sectioned to extract 65 seconds of data from each. The pre data was selected from the middle of the 3 minutes, and the post data was the 60 seconds of task and fixation as well as the last 5 seconds of the caloric condition.

ECG data were captured at 1000Hz. HR, RR-I, and other HRV indices, including the standard deviation of all normal RR-intervals (SDNN), pNN50, the square root of the mean of

the sum of the squared differences (rMSSD), and spectral parameters [normalized low-frequency power (LFNN), normalized high-frequency power (HFNN), and low-to-high-frequency ratio (LF/HF)] were derived from the ECG data using a specialized program written in MATLAB script. The HRV data were derived in accordance with the guidelines set forth by the European Society for Pacing and Electrophysiology[44].

For measurement of arterial blood pressure, continuous TBP waves were captured at a frequency of 250 Hz with the Colin 7000 radial tonometer (San Antonio, TX). The data were used to report beat-to-beat systolic and diastolic pressure. The averages for systolic and diastolic pressure for each time period sectioned were determined using MATLAB.

IC and heart sounds were used to derive SV and PEP and were used in concert with ECG and TBP tracings to derive estimates of Q and TPR. The data were collected at 1000Hz. SV was derived using the following equation: $SV = 147*(L_o^2/ Z_o^2)*(STI)*(\max dZ/dt)$ where 147 Ohms is an estimate of blood viscosity, L_0 is the length between the two electrodes across which the electrical impedance is measured, Z_0 is the impedance wave form, STI is estimated from the heart sounds tracing, and max dZ/dt is the plot of the beat-to-beat peaks of the derivative of the impedance waveform. Q was derived as the product of HR x SV, and TPR was derived as the quotient of the TBP/Q. Finally, PEP is estimated from the ECG and dp/dt (derivative of the impedance) waveforms.

Results of EOG data were measured in terms of slow-phase velocity (SPV) of the nystagmus beats[45]. SPV was calculated from the EOG waveform using the specialized MATLAB script. It incorporates both amplitude and duration information and is quantified as the number of degrees of eye excursion over a 1-second period.[43]

2.5.2 Statistical Analysis

3x2 repeated-measures ANOVA were employed to detect main effects of age (3 groups – young, middle-aged, and old) and the test time points (pre-caloric and task/fixation period) and age group by test condition interactions on HRV parameters, SV, Q, SBP, DBP, TBP, TPR, PEP, and SPV using *SPSS* software. Tukey post hoc tests were run on all significant interactions to determine group differences, and multivariate t-tests were run to determine significant changes within groups. Significance level was set at $\alpha = 0.05$

CHAPTER 3 – RESULTS

3.1 Descriptive Statistics

The table below (Table 3.1) reflects the descriptive characteristics for all participants as well as baseline data collected prior to right warm caloric stimulation. The age ranges for the participants were as follows: Young = 19-27 years; Middle-aged = 39-64 years; and Old = 79-87 years. Although baseline data for all caloric conditions are not reported here, they were similar.

Table 3.1. Mean baseline data of all subjects prior to Right Warm Caloric (RWC) stimulation.

Variable	Y (n = 11)	M (n = 7)	O (n = 9)
Age	23 ± 4	51.5 ± 12.5	83 ± 4
Height (cm)	175 ± 13.5	171.75 ± 17.25	170.5 ± 14.5
Weight (lbs)	166.25 ± 50.25	173.75 ± 45.25	177.5 ± 29.5
PRERWCLF	1319.93 ± 258.68	792.22 ± 350.25[1]	148.5 ± 285.98
PRERWCHF	588.64 ± 178.86	120.22 ± 242.18[1]	373.46 ± 197.74
PRERWCLFNN	65.59 ± 5.10	78.22 ± 6.91[1]	54.40 ± 5.64†
PRERWCHFNN	34.41 ± 5.10	21.78 ± 6.91[1]	45.60 ± 5.64†
PRERWCLF/HF	2.23 ± 0.62†	5.15 ± 0.84[1]	1.98 ± 0.69†
PRERWCRR-I	909.29 ± 36.85	824.32 ± 49.9[1]	904.95 ± 40.74
PRERWCSDNN	75.86 ± 9.23	45.06 ± 12.50[1]	34.19 ± 10.20*
PRERWCpNN50	26.76 ± 5.80	7.26 ± 7.85[1]	15.41 ± 6.41
PRERWCMSSD	52.04 ± 10.64	25.24 ± 14.41[1]	40.93 ± 11.77
PRERWCSV	138.59 ± 24.38	138.45 ± 33.01[1]	65.57 ± 26.95
PRERWCHR	67.34 ± 2.68	73.55 ± 3.63[1]	67.27 ± 2.96
PRERWCQ	9.03 ± 1.57	10.17 ± 2.12[1]	4.32 ± 1.73
PRERWCSBP	130.64 ± 6.18	136.86 ± 7.75	148.99 ± 6.83
PRERWCDBP	57.87 ± 3.87	65.50 ± 4.86	73.78 ± 4.28*
PRERWCTBP	84.06 ± 4.44	92.26 ± 5.56	102.37 ± 4.91*
PRERWCTPR	16.07 ± 3.46	12.56 ± 4.69[1]	34.91 ± 3.83*†
PRERWCSTI	0.31 ± 0.01	0.33 ± 0.12[1]	0.34 ± 0.10
PRERWCPEP	0.120 ± 0.009	0.111 ± 0.011	0.117 ± 0.010
PRERWCSPV	0.39 ± 0.06	0.42 ± 0.07	0.41 ± 0.07

Values = mean +/- SD
*Significantly different from young ($p<0.05$)
†Significantly different from middle-aged ($p<0.05$)
[1]n=6 for middle-aged

3.2 Effects of Caloric Conditions

The following two tables represent the mean effects of all caloric conditions on all subjects. Repeated measure ANOVA was used to compare these data.

Table 3.2. Mean responses of all subjects to Left Cool Caloric (LCC) and Left Warm Caloric (LWC) stimulation.

Calorics				
Variable	**LCC**		**LWC**	
	pre	**post**	**pre**	**post**
Y – LFNN	64.51 ± 4.05	64.46±5.40	62.45±5.30	61.49±5.06
M – LFNN	76.54 ± 5.48	82.81±7.31	79.13±7.18	73.07±6.85
O – LFNN	64.04 ± 4.47	59.23±5.97	57.01±5.86	54.54±5.59
Y – LF/HF	2.15 ± 0.53	2.02±0.57	2.27±0.69	1.96±0.41
M – LF/HF	4.87 ± 0.72	5.56±0.78	4.96±0.94	3.24±0.55
O – LF/HF	2.17 ± 0.59	2.82±0.63	2.27±0.77	1.74±0.45
Y – RR-I	918.53 ± 36.17	889.57±40.40	930.43±37.27	906.14±40.35†
M – RR-I	833.12 ± 48.97	828.34±54.70	833.12±50.46	824.86±54.63†
O – RR-I	900.80 ± 39.99	894.64±44.66	917.31±41.20	901.29±44.60†
Y – pNN50	31.35 ± 4.64	27.35±4.24	30.29±4.74	31.81±5.25
M – pNN50	2.24 ± 6.28	3.60±5.73	2.16±6.42	10.31±7.11
O – pNN50	9.99 ± 5.13	13.17±4.68	9.58±5.24	13.98±5.80
Y – SV	139.55 ± 25.93	131.31±23.95	136.59±24.98	135.47±24.50
M – SV	146.74 ± 35.11	162.40±32.42	149.95±33.82	155.03±33.17
O – SV	68.70 ± 28.66	66.09±26.47	63.44±27.61	69.64±27.09
Y – Q	8.97 ± 1.62	8.79±1.60	8.69±1.63	8.92±1.64†
M – Q	10.76 ± 2.19	11.94±2.16	11.05±2.21	11.39±2.22†
O – Q	4.49 ± 1.79	4.40±1.76	4.08±1.81	4.58±1.82†
Y – SBP	132.26 ± 5.17	137.10±7.19†	133.21±5.21	141.08±5.26†
M – SBP	131.44 ± 6.48	147.26±9.02†	136.50±6.53	144.57±6.60†
O – SBP	139.22 ± 5.71	146.26±7.95†	146.98±5.76	149.68±5.81†
Y – DBP	61.30 ± 3.25	66.28±3.45	63.11±3.55	64.16±3.73
M – DBP	67.06 ± 4.08	70.52±4.33	67.27±4.45	67.35±4.68
O – DBP	63.50 ± 3.60	63.45±3.82	71.90±3.93	72.71±4.13
Y – TBP	85.54 ± 3.05	90.53±4.27†	87.27±3.97	91.03±3.65
M – TBP	91.89 ± 3.82	98.95±5.36†	93.63±4.98	97.11±4.57
O – TBP	92.30 ± 3.37	94.54±4.72†	99.43±4.39	101.89±4.03
Y – TPR	19.65 ± 5.74	30.84±8.50	19.60±3.84	21.27±11.43

(Table 3.2 cont.)

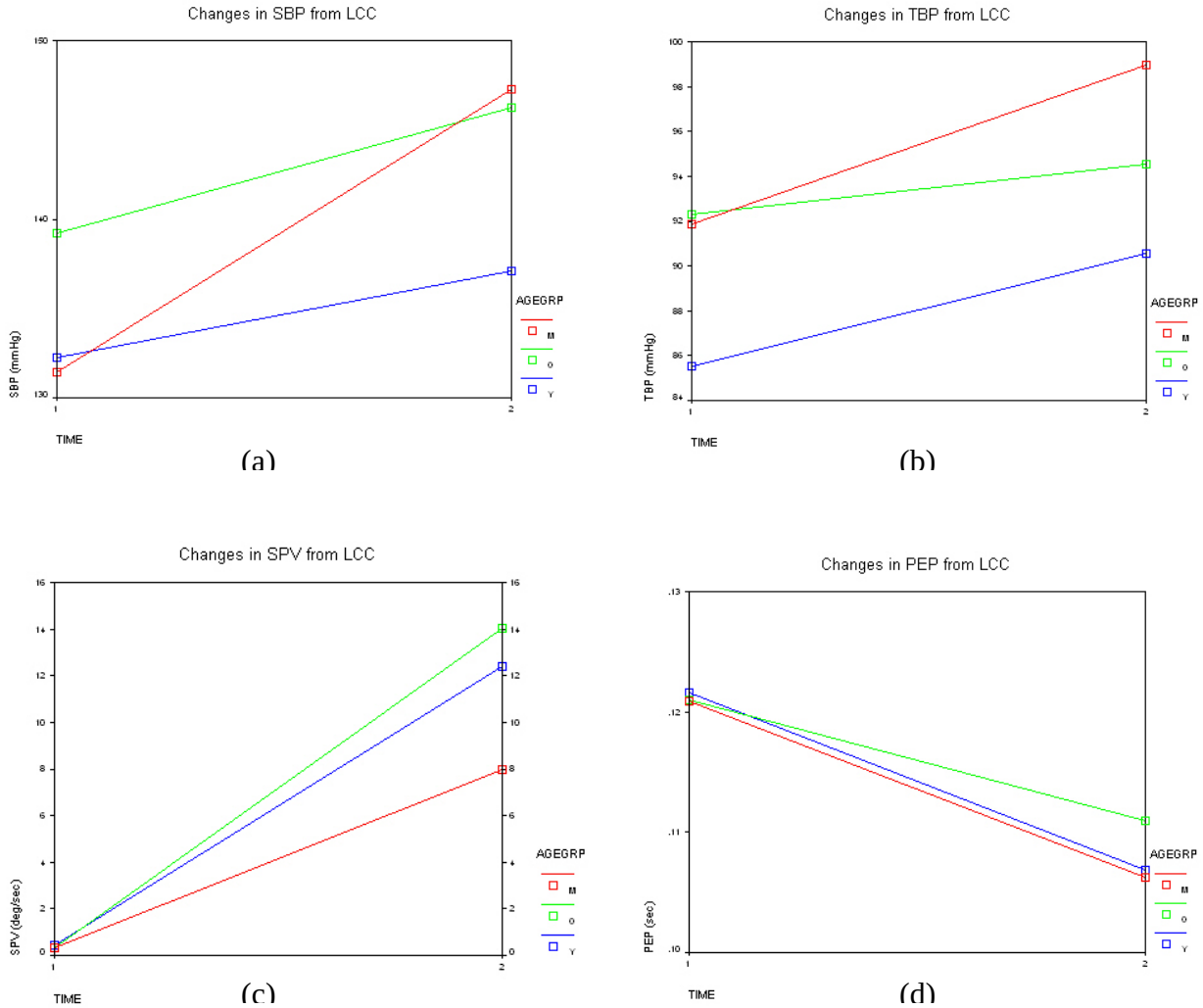
M – TPR	11.09 ± 7.78	13.45±11.51	11.75±5.20	13.01±15.48
O – TPR	34.47 ± 6.35	32.96±9.40	36.00±4.25	61.75±12.64
Y – PEP	0.122 ± 0.008	0.107±0.009†	0.120±0.008	0.108±0.007†
M – PEP	0.121±0.010	0.106±0.011†	0.121±0.010	0.107±0.009†
O – PEP	0.121±0.009	0.111±0.010†	0.125±0.009	0.115±0.008†
Y – SPV	0.46±0.06	12.39±1.50†	0.41±0.004	11.88±1.79†*
M – SPV	0.33±0.08	7.98±1.88†	0.34±0.05	6.48±2.24†*
O – SPV	0.32±0.07	14.01±1.66†	0.35±0.05	15.41±1.98†*

*Significant interaction
†Significant effect of treatment
Y = young subjects; M = middle-aged subjects; O = old subjects

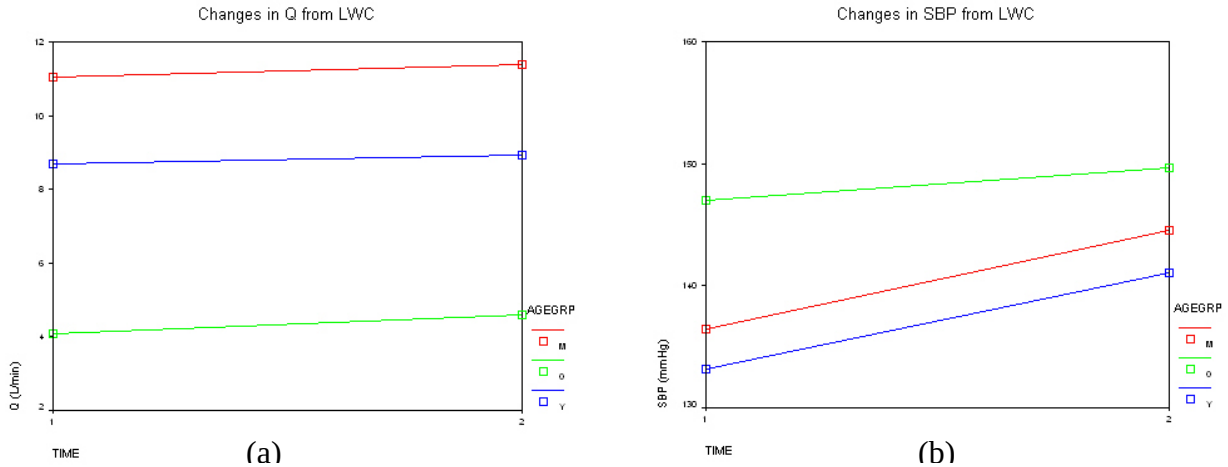
The results of the 3 x 2 repeated measures ANOVA (group x caloric treatment) revealed several significant main effects of treatment for both LCC and LWC and one group by treatment interaction for LWC.

For LCC stimulation, there were significant changes over time for all subject groups with increases in SBP (see Fig. 3.1a below), TBP (see Fig. 3.1b below), and SPV (see Fig. 3.1c below) and a decrease in PEP (see Fig. 3.1d below). LWC stimulation resulted in significant main effects of the treatment in that all subjects had increases in Q (see Fig. 3.2a below), SBP (see Fig. 3.2b below), and SPV (see Fig. 3.2c below) and a decrease in RR-I (see Fig. 3.2d below) and PEP (see Fig. 3.2e below).

There was a significant group by treatment interaction found during LWC with multivariate t-tests revealing all three subject groups had significant increases in SPV (see Fig. 3.2c below). However, post hoc tests indicated that the middle-aged group and the old group responded differently to the stressor in that the old group increased significantly more than the middle-aged group.

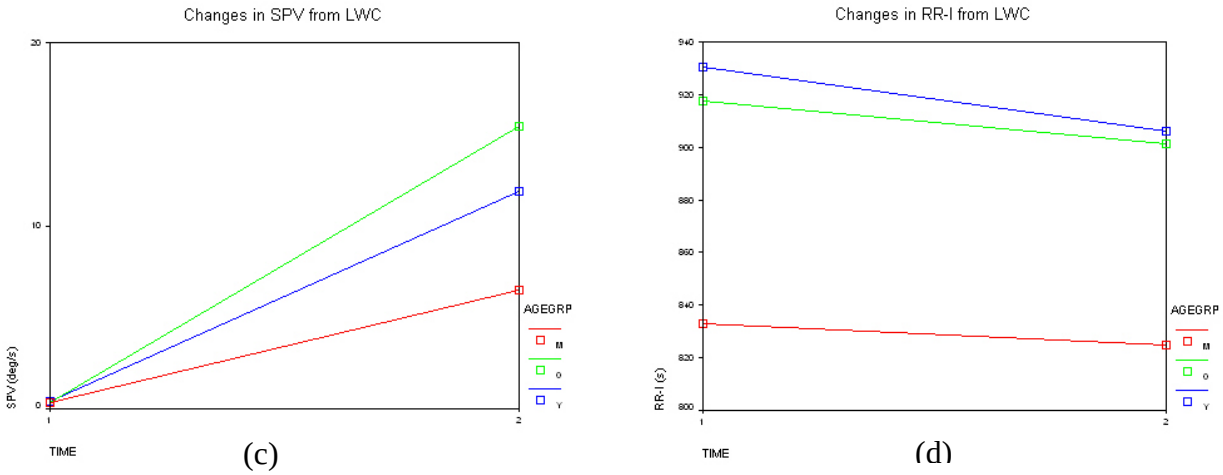


Figures 3.1a-d. Significant main effects of treatment from LCC.



Figures 3.2a-e. Significant main effects of treatment (a-e) and the significant interaction (c) from LWC.

(Fig. 3.2 cont.)



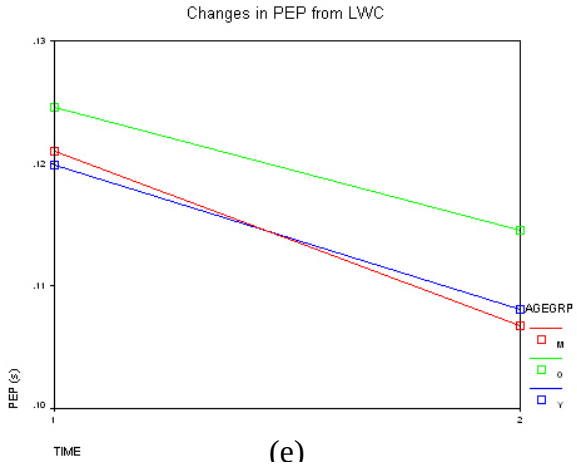


Table 3.3. Mean responses of all subjects to Right Cool Caloric (RCC) and Right Warm Caloric (RWC) stimulation.

Calorics				
Variable	**RCC**		**RWC**	
	pre	**post**	**pre**	**post**
Y – LFN	64.34 ± 6.56	58.33 ± 4.01	65.59 ± 5.10	60.05 ± 5.22
M – LFN	73.57 ± 8.47	76.92 ± 5.18	78.22 ± 6.91	78.97 ± 7.06
O – LFN	49.23 ± 6.91	60.34 ± 4.23	54.40 ± 5.64	53.05 ± 5.77
Y - LF/HF	2.55 ± 0.76	1.48 ± 0.52	2.23 ± 0.62	1.90 ± 0.73
M - LF/HF	4.16 ± 0.99	4.52 ± 0.67	5.15 ± 0.84	6.34 ± 0.99
O - LF/HF	1.99 ± 0.81	2.02 ± 0.55	1.98 ± 0.69	1.63 ± 0.81
Y – RR-I	933.60 ± 36.52	904.54 ± 41.84	909.29 ± 36.85	865.12 ± 41.69*
M – RR-I	823.08 ± 47.15	831.82 ± 54.02	824.32 ± 49.90	830.99 ± 56.44
O – RR-I	909.32 ± 38.50	889.00 ± 44.11	904.95 ± 40.74	893.92 ± 46.09

(Table 3.3 cont.)

Y - pNN50	30.16 ± 5.28	33.26 ± 5.48	26.80 ± 5.80	26.37 ± 5.80
M - pNN50	4.28 ± 6.82	6.87 ± 7.08	7.26 ± 7.85	7.44 ± 7.86
O - pNN50	13.97 ± 5.57	12.84 ± 5.78	15.41 ± 6.41	17.21 ± 6.42
Y – SV	147.87 ± 27.41	138.33 ± 24.34	138.59 ± 24.38	134.42 ± 24.07
M – SV	139.86 ± 35.38	154.16 ± 31.42	138.45 ± 33.01	150.32 ± 32.59
O – SV	67.50 ± 28.89	68.52 ± 25.65	65.57 ± 26.95	65.36 ± 26.61
Y – Q	9.46 ± 1.78	9.27 ± 1.67	9.03 ± 1.57	9.03 ± 1.58
M – Q	10.34 ± 2.30	11.15 ± 2.15	10.17 ± 2.12	11.12 ± 2.13
O – Q	4.35 ± 1.88	4.58 ± 1.76	4.32 ± 1.73	4.38 ± 1.74
Y – SBP	133.30 ± 5.57	141.41 ± 6.87†	130.64 ± 6.18	138.44 ± 6.19†
M – SBP	135.39 ± 6.99	146.59 ± 8.62†	136.86 ± 7.75	141.87 ± 7.76†
O – SBP	142.98 ± 6.16	142.16 ± 7.60†	148.99 ± 6.83	156.10 ± 6.84†
Y – DBP	64.67 ± 3.40	70.67 ± 4.92	57.87 ± 3.87	67.57 ± 3.85†*
M – DBP	69.26 ± 4.26	70.35 ± 6.17	65.50 ± 4.86	65.85 ± 4.82†
O – DBP	65.24 ± 3.76	67.34 ± 5.44	73.78 ± 4.28	76.01 ± 4.25†
Y – TBP	88.33 ± 3.48	96.05 ± 4.85†	84.06 ± 4.44	92.81 ± 4.55†
M – TBP	95.17 ± 4.36	102.32 ± 6.08†	92.26 ± 5.56	95.43 ± 5.71†
O – TBP	93.26 ± 3.85	95.85 ± 5.36†	102.37 ± 4.91	106.68 ± 5.03†
Y – TPR	17.57 ± 7.62	25.52 ± 4.49	16.07 ± 3.46	86.20 ± 44.69
M – TPR	12.37 ± 9.84	18.97 ± 5.79	12.56 ± 4.69	12.99 ± 60.51
O – TPR	41.42 ± 8.04	31.44 ± 4.73	34.91 ± 3.83	42.55 ± 49.41
Y – PEP	0.123 ± 0.008	0.107 ± 0.007†	0.120 ± 0.009	0.110 ± 0.007†
M – PEP	0.122 ± 0.010	0.105 ± 0.009†	0.111 ± 0.011	0.104 ± 0.009†
O – PEP	0.115 ± 0.009	0.110 ± 0.008†	0.117 ± 0.010	0.105 ± 0.008†
Y – SPV	0.41 ± 0.06	12.16 ± 1.88†	0.39 ± 0.06	12.16 ± 1.14†*
M – SPV	0.34 ± 0.08	5.90 ± 2.35†	0.42 ± 0.07	6.59 ± 1.42†*
O – SPV	0.45 ± 0.07	12.74 ± 2.08†	0.41 ± 0.07	13.05 ± 1.26†*

*Significant interaction
†Significant effect of treatment
Y = young subjects; M = middle-aged subjects; O = old subjects

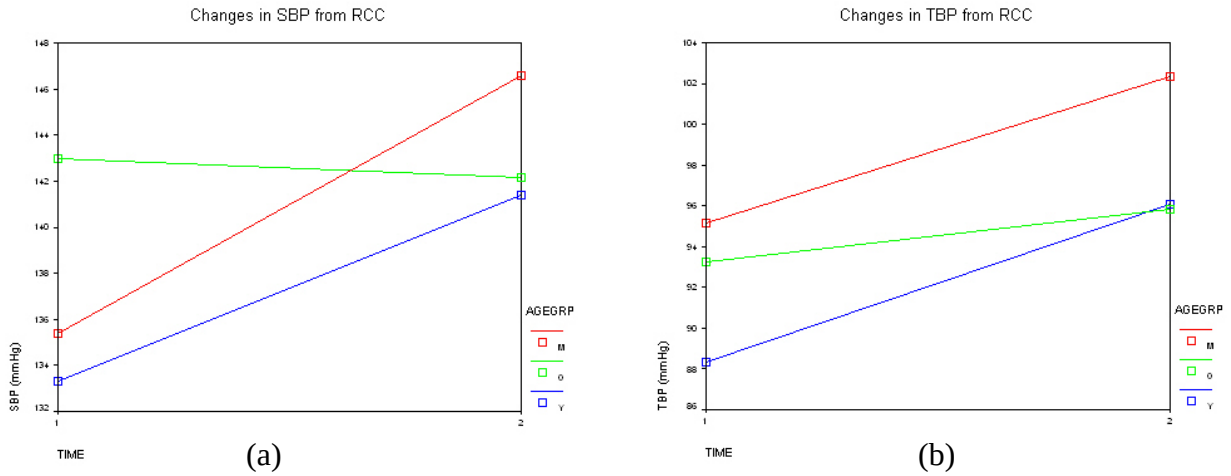
The results of the 3 x 2 repeated measures ANOVA (group x caloric treatment) revealed several significant main effects of treatment for both RCC and RWC and three group by treatment interactions for RWC.

For RCC (Fig. 3.3) and RWC (Fig. 3.4) stimulations, there were significant main effects of the treatment for SBP (see Figs. 3.3a and 3.4a below), TBP (see Figs. 3.3b and 3.4b below),

PEP (see Figs. 3.3c and 3.4c below), and SPV (see Figs. 3.3d and 3.4d below) in that all subjects had increases in SBP, TBP, and SPV and a decrease in PEP for both conditions. RWC stimulation also yielded an increase over time for DBP (see Fig. 3.4e below).

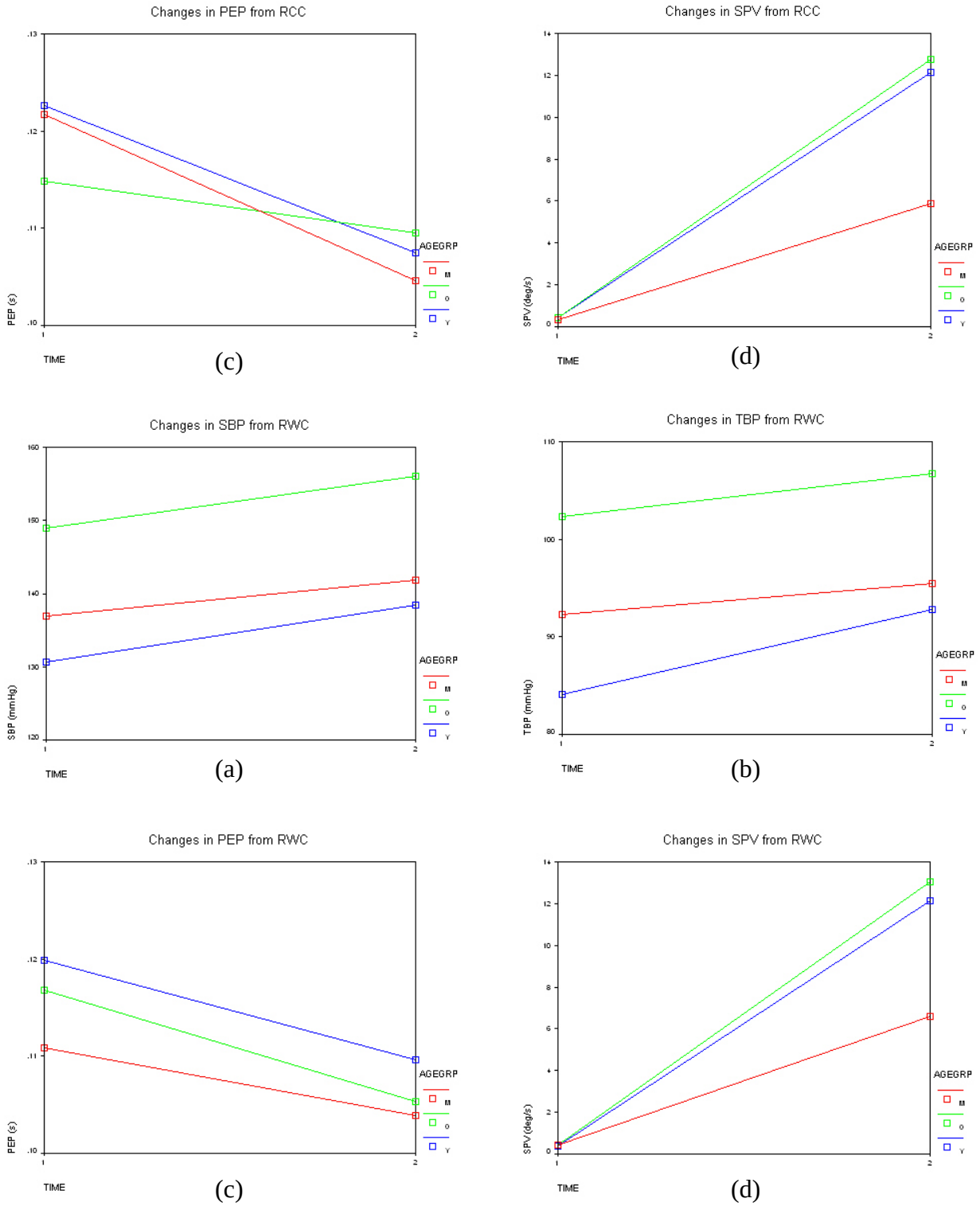
The illustration of SBP during RCC (Fig. 3.3a) suggests a possible age group by treatment interaction insofar as the mean score for the old subject group does not increase, and in fact appears to decrease. However, the interaction term did not approach significance. Rather, this was the result of one point of influence among the cases of older adults where the subject had a high pre-test SBP and a sharp drop in SBP following caloric irrigation. The other cases of older adults typically resulted in small increases in SBP.

There were, however, three significant group by treatment interactions during RWC. These include SPV (see Fig. 3.4d below), DBP (see Fig. 3.4e below), and RR-I (see Fig. 3.4f below). Multivariate t-tests revealed that only the young group actually had a significant change for DBP (an increase) and RR-I (a decrease), but all groups had a significant increase in SPV during RWC. The post hoc tests indicated no significant differences between the groups for RR-I and DBP, but they did show that SPV for the young and old groups increased significantly more than SPV did in the middle-aged group (see Fig. 3.4d below).



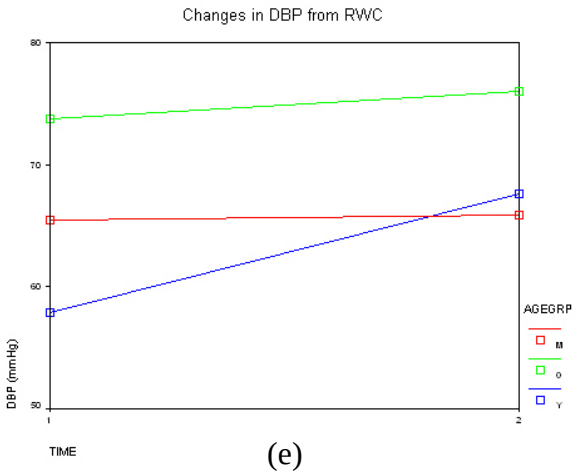
Figures 3.3a-d. Significant main effects of treatment from RCC.

(Fig. 3.3 cont.)

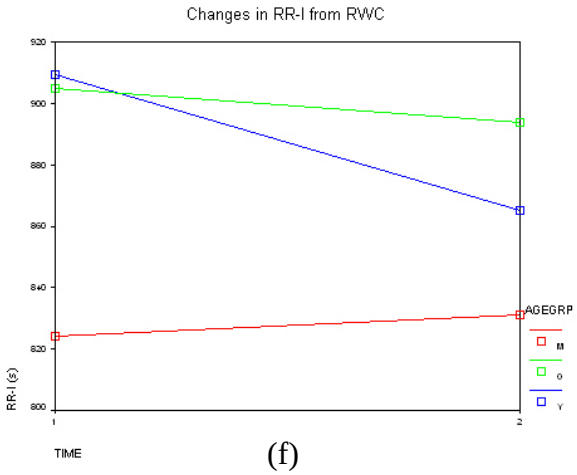


Figures 3.4a-f. Significant main effects of treatment (a-f) and significant interactions (d-f) from RWC.

(Fig. 3.4 cont.)



(e)



(f)

Table 3.4 below includes a summary of all main effects and significant interactions found from VSR excitation through caloric stimulation on both cardiovascular and ocular parameters.

Table 3.4. Effects of Treatment on Cardiovascular and Ocular Measures

	LCC		LWC		RCC		RWC	
	Main	Interact	Main	Interact	Main	Interact	Main	Interact
RR-I			↓					✓
SBP	↑		↑		↑		↑	
DBP							↑	✓
TBP	↑				↑		↑	
Q			↑					
SV								
PEP	↓		↓		↓		↓	
STI								
LFNN								
LF/HF								
SDNN								
pNN50								
SPV	↑		↑	✓	↑		↑	✓

↑ Indicates a significant main effect of treatment observed as an increase over time
↓ Indicates a significant main effect of treatment observed as a decrease over time
✓ Significant group by treatment interaction observed

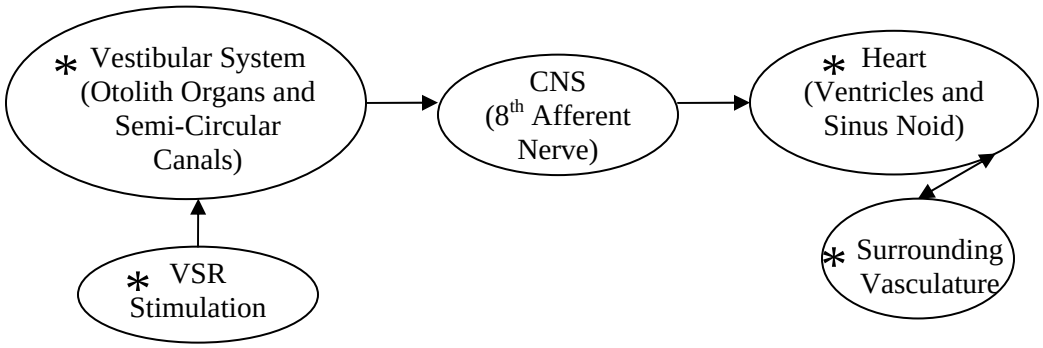
CHAPTER 4 – DISCUSSION

The present investigation was designed to examine cardiovascular and ocular responses to caloric stimulation of the semi-circular canals. The observed baseline values for cardiovascular and ocular parameters were in the range of expected values for each age group[46] in that pressure and resistance values increased with age (see Table 3.1). There was one exception. The LF/HF for the middle-aged subjects was much higher than the expected baseline value, which may be due to a few outliers as well as the fact that these data were collected using indirect measures in an unstable situation (to be explained further below). The values found from caloric stimulation were also in the range of expected values with only a couple of exceptions (see Tables 3.2 and 3.3). While HRV parameters are consistent with other published data from our lab, Wood et al.[47], and blood pressure and HR data are consistent with Ray et al.[10] and Monhan et al.[27] – when considering age-related variances – the values for Q and SV are higher than expected. This is a result of using IC, which is thought to be a useful tool for examining within subjects changes in Q and SV but does not provide a particularly precise measure of Q and SV.

In comparing our subjects to those of previous studies investigating age and the VSR, an important difference is noted with regard to the age range of the subjects. All of the other studies either had only young subjects (under 35 years) or young (under 35 years) and old (63 – 65 years) subjects. The present study not only used older subjects for the "old" group (79 – 87 years), but also included a middle-aged group (39 – 64 years) for additional comparisons.

With respect to the specific aims of the investigation, we hypothesized that we would find a main effect of treatment such that excitation of the semi-circular canals would result in stimulation of the VSR and, consequently, sympathetic activation (see Fig. 4.1 below).

Furthermore, we expected the younger subjects to exhibit greater cardiovascular changes resulting from this sympathetic activation than the older subjects. We also expected to see significant increases in SPV for all subjects.



* Age affects the structure and functionality. As noted in the introduction, aging causes degeneration in the vestibular and cardiovascular systems, and it also leads to an attenuation of the VSR.

Fig. 4.1. Sequence of the affects of VSR stimulation in a healthy functioning body.

Our data and research indicate that there is VSR stimulation through excitation of the semi-circular canals (see Fig. 4.1 above). In order to ensure the stimulus was sufficient to evoke a response, we measured SPV. As expected, we found significant increases in SPV for all subjects under all conditions (see Tables 3.2 and 3.3), which indicate adequate excitation of the semi-circular canals to stimulate the VSR. Interestingly, we found greater increases in SPV in the old subjects than the middle-aged or young subjects, yet, overall, the old subjects showed smaller cardiac responses (see Table 3.4). This is possibly due to a lack of inhibition within the vestibular system due to normal aging degeneration causing a greater ocular response. Their cardiovascular systems, however, still exhibited expected smaller responses than the other groups due to alterations in both the structures (i.e. vascular stiffness) and functionality (i.e. abnormalities in blood pressure regulation). With respect to indices of cardiovascular sympathetic activation, we observed, across the four conditions (LCC, LWC, RCC and RWC),

evidence of sympathetic activation as seen by increases in HR (not reported but implied from the decreases seen in RR-I) and TBP as well as decreases in PEP, RR-I, and Q (with some exceptions) from excitation of the semi-circular canals (see Tables 3.2 and 3.3).

Cui et al.[24,25] also used caloric testing for their studies and found similar results as ours – an increase in both HR and blood pressure with excitation of the semi-circular canals. However, they only had "young" subjects (under 35 years), and their "warm" and "cool" temperatures were both significantly lower (44°C and 10°C) than those we used (50°C and 24°C). Because they used water instead of air, as we did, we were likely to have similar results between the two studies for the warm temperatures, but slightly different outcomes for the cool temperatures. Research by audiologists has shown that cooler water temperatures than air cause similar magnitudes of nystagmus SPV, but water media results in a longer response duration[43] yielding similar responses with 44°C water irrigations and 50°C air irrigations. This may also affect cardiovascular responses. Further research needs to be done to determine any variances in outcomes and excitation levels from less and more extreme temperature ranges for caloric stimulation.

While the studies by Cui et al.[24,25] indicate sympathetic activation through excitation of the VSR, studies by both Costa et al.[26] and Ray et al.[27] did not. However, Costa et al.[26] only had five subjects, and they only used cool temperatures. This likely indicates a lack of power because of the lack of subjects. This lends the possibility that if they had used more subjects, they may have found results more similar to ours. Also, although we saw evidence of sympathetic activation with semi-circular excitation using both cool and warm temperatures, we found more significant changes (and interactions) using the warm temperature (see Table 3.4). One possible explanation of these differences is that the peripheral changes caused by warm air

caloric stimulation cause greater central responses than the cool air. The warm air could trigger vasodilation, which leads to a decrease in blood pressure and an increase in heart rate as well as a decrease in RR-I. However, the body works diligently to defend blood pressure, and with as previously discussed, younger subjects generally have fewer issues with cardiovascular dysfunction. This could explain the overall increase in blood pressure (TBP), with the younger subjects having greater responses than the old subjects. If Costa et al.[26] had also used a warm temperature; again, they may have come to a different conclusion.

Ray et al.[27] used yaw head rotation (YHR) instead of caloric stimulation to excite the semi-circular canals. When comparing our preliminary data using headshakes with their data, we believe they simply did not use enough stimulation. We used 1.7 Hz and 2.4 Hz, while the highest they went was 1.0 Hz. Also important to note about their data is that at 1.0 Hz (their greatest level of stimulation) they were starting to see increases in HR and blood pressure – just not enough to be significant. If they had further investigated these increases, as we did, with faster head movements (greater stimulation), they likely would have found similar results as ours and had a different conclusion: that semi-circular canal excitation does stimulate the VSR, and, thus leads to sympathetic activation and the corresponding cardiovascular changes.

We also hypothesized that age would be inversely related to the magnitude of response in our participants. The data appear to support our hypothesis to some extent (see Tables 3.2, 3.3, and 3.4). Our results indicate that younger subjects defended TBP to a greater extent than the older subjects in that the younger subjects had greater increases in TBP with caloric stimulation than the older subjects. Overall, young subjects had noticeably greater changes than the middle-aged and old subjects in the majority of cardiac parameters considered – TBP, SV, PEP and RR-I (see Tables 3.2 and 3.3). This supports our hypothesis that there are age-related disparities in

cardiac chronotropic activity with semi-circular canal excitation through VSR stimulation – quite possibly due to an attenuation of the VSR with age as previously hypothesized and shown by Ray et al.[11] with respect to otolithic activation. Another possible explanation of these differences in responses is that there are age-related changes in physiology and overall functional status that lead to increases in HR and TBP and likely also play a role, along with the VSR, in yielding these diversities. Aging has been shown to result in marked abnormalities of cardiovascular regulation due to alterations in the structure and function of the heart and vasculature, including vascular stiffness, which leads to elevated systolic arterial pressure as well as augmented aortic impedance and cardiac mechanical load. Some of the functional changes also occur in the coronary vasculature, which yields a gradual age-associated decline in coronary flow reserve[48]. These changes may have considerable consequences during superimposed cardiovascular stress, which we believe has been shown to occur through stimulation of the VSR and yields these differences in cardiovascular response with age.

This study is not without its limitations, most of which relate to limitations in the measure of autonomic nervous system activity. It is impossible to directly measure sympathetic nervous system activation in humans. Consequently, we must rely on indirect methods of measurement, such as HRV. HRV assumes the branches of the heart behave similarly on both sides. Unfortunately, this is not always the case. HRV is also not designed to follow changes with HR, but just to determine the various parameters during a stable situation. Thus, there are possible discrepancies, at least in the absolute values, of our data and possibly, to some extent, in the trends.

IC, used to determine SV and Q, is also an indirect method of measurement and should be used more as an index of measure to determine trends rather than a source of absolute values.

SV and Q were determined according to the specifications of *Biopac*, but IC is still not the best source of absolute values. Fortunately, trends can still show age-related disparities and are an acceptable use of IC.

Another issue is that caloric testing causes dizziness and sometimes nausea, which also lead to sympathetic activation. Although many subjects did mention feeling varying degrees of dizziness throughout the testing, only a couple of them actually became nauseated from the testing. Costa et al.[26] noted in their study that they did not find significant changes in HR, blood pressure, or MSNA with caloric stimulation, even with nausea and dizziness. Although there are issues of power with their study, it is interesting to cite this lack of sympathetic activation from nausea and dizziness due to caloric stimulation.

Our most significant limitation is the lack of use of our control data. We do not have the data to prove that there was or was not cognitive interference due to fear and/or apprehension of the caloric stimulations, which would cause similar responses as those we perceived as a result of VSR stimulation. If the control data were to show no significant cardiovascular responses, then our results and conclusions are more likely to be accurate. Unfortunately, we do not have the necessary data to prove this.

One other possible limitation of the present data set is that the analyses are not well-powered yet. Although we had more age groups and subjects than the others using calorics (two fewer than Ray et al.[27], though), each group had a small "n". Because of this, we must remain inconclusive about the age-related disparities we discovered.

In conclusion, we found that semi-circular canal excitation may stimulate the VSR yielding sympathetic activation with the corresponding cardiac chronotropic activity including an increase in TBP and HR and decreases in RR-I, PEP, and Q.

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APPENDIX – NOTE ON IMPEDANCE CARDIOGRAPHY

CHAPTER 1 – INTRODUCTION

1.1 Cardiothoracic Impedance

Cardiac output measures the volume of blood pumped by the heart per minute[1]. It is an assessment tool used to determine circulation stasis of an individual, and is therefore important for our purposes because of the implications circulation (or lack thereof) have on blood pressure.

Ray et al.[2,3,4] did not, however, measure cardiac output on their subjects, likely due to the complexity and expense associated with employing direct measures of cardiac output in humans. Fortunately, there are indirect ways of estimating cardiac output, which include the technique of cardiothoracic impedance. This is a non-invasive, low-cost approach used to derive estimates of stroke volume, cardiac output, and systolic time intervals, while requiring minimal technical expertise and providing continual hemodynamic measurements with no risk to the subject. Impedance is used by passing a small, high frequency current through the thorax by way of electrodes stuck directly to the skin. Investigators have previously reported the reliability of a variety of cardiothoracic impedance devices under a variety of situations to allow non-invasive but accurate measurements of stroke volume and cardiac output[1,5]. However, cardiac impedance methods have been discounted by studies involving critical care and emergency patients due to a significant number of inaccurate readings[6]. Impedance cardiography has also been tested to determine reliability in tracking expected hemodynamic responses to drugs, and it consistently followed the course predicted by the behavioral effect of the drug[7]. The purpose of this investigation is to measure the test-retest reliability of cardiac output and stroke volume as measured with impedance cardiography using the *Biopac* cardiothoracic amplifier and the *Acknowledge* software (Santa Barbara, CA) under the following conditions: lying prone, head-

down neck flexion, lying supine, and 70° up-right tilt. This information is important to further validate any data obtained from a more comprehensive study designed to demonstrate the effects of vestibular dysfunction in the elderly on the cardiovascular system – specifically cardiac output and stroke volume – as another indicator of disease and/or disease risk. Based on Koobi et al.[5] and Theisen et al.[8] we hypothesize that we will find reliability coefficients for stroke volume and cardiac output in the range of 0.74 & 0.977.

CHAPTER 2 – METHODS

2.1 Instruments

The impedance cardiograph data will be collected and processed via Biopac data amplifiers and analog to digital board (Santa Barbara, CA). The Biopac signals are digitized and stored with the use of the companion Acknowledge 3.7.2 software (Santa Barbara, CA). The tonometric blood pressure data will be captured using the Colin 7000 tonometric blood pressure device (San Antonio, TX). This device also has a voltage output that is sent to the Biopac AD board and is digitized and stored in real time along with the other physiologic signals. The Biopac equipment for cardiac output measurement incorporates a precision high-frequency current source, which introduces a very small (100μA rms or 400μA rms) current through the tissue being measured (heart and surrounding thorax tissue) with the volume being defined by the placement of a set of current source electrodes. A separate set of monitoring electrodes then measures the voltage developed across the tissue volume. Because the current is constant, the voltage measured is proportional to the characteristics of the biological impedance of the tissue volume.

2.2 Procedures

2.2.1 Lead Placement

When using the *Biopac* EBI100C for cardiac impedance, four of the CBL204 Touchproof "Y" electrodes are used as lead adapters and eight of the LEAD110 electrode leads are connected to EL500 paired, disposable electrodes. The two top-neck electrodes are connected to the Iout jack on the EBI100C. The bottom-torso electrodes are connected to the Iin jack on the EBI100C. The inner (upper and lower) sets of voltage sensing electrodes are connected to Vin+ and Vin- respectively.

A study published in 1996 by Woltjer et al.[9] focused on determining the best combination of two electrode arrays (lateral versus semi-circular) and two equations (Kubicek versus Sramek-Bernstein). The normal set-up is the lateral array with the Kubicek equation. However, according to Woltjer et al.[9], using the semi-circular spot array with the Kubicek equation provides the most accurate and reliable stroke volume measurements when compared to thermodilution (the "gold standard" for invasive cardiac output and stroke volume measurement). We used the normal set-up, though, because the equipment we have does not include the capacity to use nine electrodes – the necessary amount for the semi-circular spot array.

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VITA

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